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(54) Title: EXTENDED-RELEASE FORMULATION FOR REDUCING THE FREQUENCY OF URINATION AND METHOD OF USE THEREOF

(57) Abstract: A method for reducing the frequency of urination is disclosed. The method comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising one or more analgesic agents and one or more a-b lockers. In one embodiment, the one or more analgesic agents are formulated for extended-release.

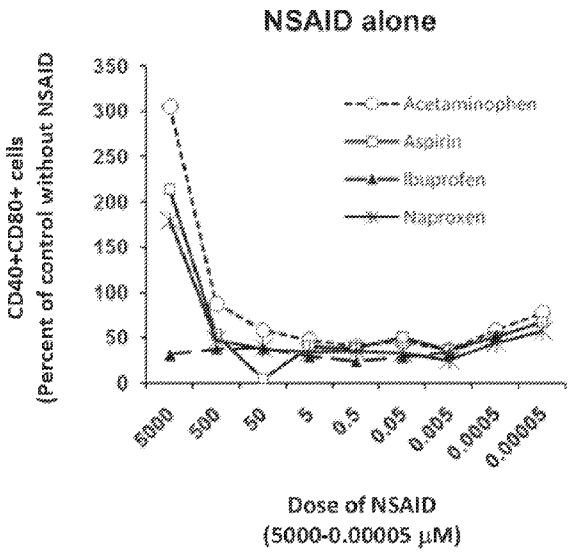

FIG. 1A

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TITLE

EXTENDED-RELEASE FORMULATION FOR REDUCING THE FREQUENCY OF URINATION AND METHOD OF USE THEREOF

[0001] This application claims priority from U.S. Patent Application Serial No. 13/487,348, filed June 4, 2012 and U.S. Patent Application Serial No. 13/424,000, filed March 19, 2012.

FIELD

[0002] The present application generally relates to methods and compositions for inhibiting the contraction of muscles and, in particular, to methods and compositions for inhibiting the contraction of smooth muscles of the urinary bladder.

BACKGROUND

[0003] The detrusor muscle is a layer of the urinary bladder wall made of smooth muscle fibers arranged in spiral, longitudinal, and circular bundles. When the bladder is stretched, this signals the parasympathetic nervous system to contract the detrusor muscle. This encourages the bladder to expel urine through the urethra.

[0004] For the urine to exit the bladder, both the autonomically controlled internal sphincter and the voluntarily controlled external sphincter must be opened. Problems with these muscles can lead to incontinence. If the amount of urine reaches 100% of the urinary bladder's absolute capacity, the voluntary sphincter becomes involuntary and the urine will be ejected instantly.

[0005] The human adult urinary bladder usually holds about 300-350 ml of urine (the working volume), but a full adult bladder may hold up to about 1000 ml (the absolute volume), varying among individuals. As urine accumulates, the ridges produced by folding of the wall of the bladder (rugae) flatten and the wall of the bladder thins as it stretches, allowing the bladder to store larger amounts of urine without a significant rise in internal pressure.

[0006] In most individuals, the desire to urinate usually starts when the volume of urine in the bladder reaches around 200 ml. At this stage it is easy for the subject, if desired, to resist the urge to urinate. As the bladder continues to fill, the desire to urinate becomes stronger and harder to ignore. Eventually, the bladder will fill to the point where the urge to urinate becomes overwhelming, and the subject will no longer be able to ignore it. In some individuals, this desire to urinate starts when the bladder is less than 100% full in relation to its working volume. Such increased desire to urinate may interfere with normal activities, including the ability to sleep for sufficient uninterrupted periods of rest. In some cases, this

increased desire to urinate may be associated with medical conditions such as benign prostate hyperplasia or prostate cancer in men, or pregnancy in women. However, increased desire to urinate also occurs in individuals, both male and female, who are not affected by another medical condition.

[0007] Accordingly, there exists a need for compositions and methods for the treatment of male and female subjects who suffer from a desire to urinate when the bladder is less than 100% full of urine in relation to its working volume. Said compositions and methods are needed for the inhibition of muscle contraction in order to allow in said subjects the desire to urinate to start when the volume of urine in the bladder exceeds around 100% of its working volume.

SUMMARY

[0008] One aspect of the present application relates to a method for reducing the frequency of urination in a subject. The method comprises administering to a subject in need thereof an effective amount of one or more analgesic agents, and an effective amount of one or more additional active ingredients selected from the groups consisting of α-blockers and 5α-reductase inhibitors. The method can be used for the treatment of nocturia or overactive bladder

[0009] Another aspect of the present application relates to a pharmaceutical composition comprising an active ingredient comprising one or more analgesic agents, an α-blocker, and a pharmaceutically acceptable carrier.

[0010] Another aspect of the present application relates to a pharmaceutical composition comprising an active ingredient comprising one or more analgesic agents, a 5α-reductase inhibitor, and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF DRAWINGS

[0011] Figure 1A and 1B are diagrams showing that analgesics regulate expression of co-stimulatory molecules by Raw 264 macrophage cells in the absence (Figure 1A) or presence (Figure 1B) of LPS. Cells were cultures for 24 hrs in the presence of analgesic alone or together with *Salmonella typhimurium* LPS (0.05 μg/ml). Results are mean relative % of CD40+CD80+ cells.

DETAILED DESCRIPTION

[0012] The following detailed description is presented to enable any person skilled in the art to make and use the invention. For purposes of explanation, specific nomenclature is set forth to provide a thorough understanding of the present invention. However, it will be

apparent to one skilled in the art that these specific details are not required to practice the invention. Descriptions of specific applications are provided only as representative examples. The present invention is not intended to be limited to the embodiments shown, but is to be accorded the broadest possible scope consistent with the principles and features disclosed herein.

[0013] As used herein, the term "an effective amount" means an amount necessary to achieve a selected result.

[0014] As used herein, the term "analgesic" refers to agents, compounds or drugs used to relieve pain and inclusive of anti-inflammatory compounds. Exemplary analgesic and/or anti-inflammatory agents, compounds or drugs include, but are not limited to, the following substances: non-steroidal anti-inflammatory drugs (NSAIDs), salicylates, aspirin, salicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, para-aminophenol derivatives, acetanilide, acetaminophen, phenacetin, fenamates, mefenamic acid, meclofenamate, sodium meclofenamate, heteroaryl acetic acid derivatives, tolmetin, ketorolac, diclofenac, propionic acid derivatives, ibuprofen, naproxen sodium, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin; enolic acids, oxicam derivatives, piroxicam, meloxicam, tenoxicam, ampiroxicam, droxicam, pivoxicam, pyrazolon derivatives, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone, coxibs, celecoxib, rofecoxib, nabumetone, apazone, indomethacin, sulindac, etodolac, isobutylphenyl propionic acid, lumiracoxib, etoricoxib, parecoxib, valdecoxib, tiracoxib, etodolac, darbufelone, dexketoprofen, aceclofenac, licofelone, bromfenac, loxoprofen, pranoprofen, piroxicam, nimesulide, cizolirine, 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one, meloxicam, lornoxicam, d-indobufen, mofezolac, amtolmetin, pranoprofen, tolfenamic acid, flurbiprofen, suprofen, oxaprozin, zaltoprofen, alminoprofen, tiaprofenic acid, pharmacological salts thereof, hydrates thereof, and solvates thereof.

[0015] As used herein, the terms "coxib" and "COX inhibitor" refer to a composition of compounds that is capable of inhibiting the activity or expression of COX2 enzymes or is capable of inhibiting or reducing the severity, including pain and swelling, of a severe inflammatory response.

[0016] As used herein, the term "derivative" refers to a chemically modified compound wherein the modification is considered routine by the ordinary skilled chemist, such as an ester or an amide of an acid, protecting groups, such as a benzyl group for an alcohol or thiol, and tert-butoxycarbonyl group for an amine.

[0017] As used herein, the term "analogue" refers to a compound which comprises a chemically modified form of a specific compound or class thereof, and which maintains the pharmaceutical and/or pharmacological activities characteristic of said compound or class.

[0018] As used herein "subject" or "patient" encompasses mammals. In one aspect, the mammal is a human. In another aspect, the mammal is a non-human primate such as chimpanzee, and other apes and monkey species. In one aspect, the mammal is a domestic animal such as rabbit, dog, or cat. In another aspect, the mammal is a farm animal such as cattle, horse, sheep, goat, or swine. In another aspect, the mammal is a laboratory animal, including rodents, such as rats, mice and guinea pigs, and the like.

[0019] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluensulfonic, methanesulfonic, ethane dislfonic, oxalic, isethionic, and the like.

[0020] As used herein, the phrase "pharmaceutically acceptable" is used with reference to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

[0021] The urinary bladder has two important functions: storage of urine and emptying. Storage of urine occurs at low pressure, which implies that the detrusor muscle relaxes during the filling phase. Emptying of the bladder requires a coordinated contraction of the detrusor muscle and relaxation of the sphincter muscles of the urethra. Disturbances of the storage function may result in lower urinary tract symptoms, such as urgency, frequency, and urge incontinence, the components of the overactive bladder syndrome. The overactive bladder syndrome, which may be due to involuntary contractions of the smooth muscle of the

bladder (detrusor) during the storage phase, is a common and underreported problem, the prevalence of which has only recently been assessed.

[0022] One aspect of the present application relates to a method for reducing the frequency of urination. The method comprises administering to a subject in need thereof an effective amount of one or more analgesic agents, and an effective amount of an α-blocker. In some embodiments, the one or more analgesic agents and the α-blocker are administered separately in different dosage forms. In other embodiments, the one or more analgesic agents and the α-blocker are administered simultaneously in a single dosage form (e.g., in a single pill or tablet). In some embodiments, both the one or more analgesic agents and the α-blocker are formulated for immediate release after administration. In other embodiments, both the one or more analgesic agents and the α-blocker are formulated for delayed- release after administration. In other embodiments, both the one or more analgesic agents and the α-blocker are formulated for extended release after administration. In other embodiments, both the one or more analgesic agents and the α-blocker are formulated for delayed-extended release after administration. In other embodiments, the one or more analgesic agents are formulated for delayed-release, extended release or delayed extended release, and the α-blocker is formulated for immediate release. In yet other embodiments, the one or more analgesic agents are formulated for immediate release, and the α-blocker is formulated for delayed-release, extended release or delayed extended release. The method can be used for the treatment of nocturia or overactive bladder. Another aspect of the present application relates to a pharmaceutical composition comprising an active ingredient comprising one or more analgesic agents, an α-blocker, and a pharmaceutically acceptable carrier.

[0023] Alpha-blockers, also called α-adrenergic-antagonists or α-blockers, are pharmacological agents that act as receptor antagonists of α-adrenergic receptors, which are further divided into α1-adrenergic receptors and α2-adrenergic receptors. Alpha blockers can be classified as selective blockers that selectively act at α1-adrenoceptors or α2-adrenoceptors, and non-selective alpha blockers that act at both types of α-adrenergic receptors.

[0024] Examples of selective α1-adrenergic blockers include, but are not limited to, alfuzosin, prazosin, doxazosin, tamsulosin, terazosin, carvedilol, labetalol and silodosin. Examples of selective α2-adrenergic blockers include, but are not limited to, atipamezole, idazoxane and yohimbine. Examples of non-selective α-adrenergic blockers include: phenoxybenzamine, phentolamine, tolazoline, trazodone, typical and atypical antipsychotics.

[0025] In some embodiments, the one or more analgesic agents are administered orally in an individual or combined daily dose of 50-2000 mg, 50-1500 mg, 50-1200 mg, 50-1000 mg, 50-800 mg, 50-600 mg, 50-500 mg, 50-400 mg, 50-300 mg, 50-250 mg, 50-200 mg, 50-100 mg, 100-2000 mg, 100-1500 mg, 100-1200 mg, 100-1000 mg, 100-800 mg, 100-600 mg, 100-500 mg, 100-400 mg, 100-300 mg, 100-200 mg, 200-2000 mg, 200-1500 mg, 200-1200 mg, 200-1000 mg, 200-800 mg, 200-600 mg, 200-400 mg, 400-2000 mg, 400-1500 mg, 400-1200 mg, 400-1000 mg, 400-800 mg, 400-600 mg, 600-2000 mg, 600-1500 mg, 600-1200 mg, 600-1000 mg, 600-800 mg, 800-2000 mg, 800-1500 mg, 800-1200 mg, 800-1000 mg, 1000-2000 mg, 1000-1500 mg, 1000-1200 mg, 1200-2000 mg, 1200-1500 mg or 1500-2000 mg; and the one or more α-blockers are administered orally in an individual or combined daily dose of between 0.01-100 mg, 0.01-30 mg, 0.01-10 mg, 0.01-3 mg, 0.01-1 mg, 0.01-0.3 mg, 0.01-0.1 mg, 0.01-0.03 mg, 0.03-100 mg, 0.03-30 mg, 0.03-10 mg, 0.03-3 mg, 0.03-1 mg, 0.03-0.3 mg, 0.03-0.1 mg, 0.1-100 mg, 0.1-30 mg, 0.1-10 mg, 0.1-3 mg, 0.1-1 mg, 0.1-0.3 mg, 0.3-100 mg, 0.3-30 mg, 0.3-10 mg, 0.3-3 mg, 0.3-1 mg and 0.2-1 mg.

[0026] In some embodiments, the α-blocker is a non-selective α-blocker. In other embodiments, the α-blocker is a selective α1-adrenergic blocker. In other embodiments, the α-blocker is a selective α2-adrenergic blocker. In other embodiments, the α-blocker is tamsulosin.

[0027] Another aspect of the present application relates to a pharmaceutical composition comprising: one or more analgesic agents; one or more α-blockers; and a pharmaceutically acceptable carrier. In some embodiments, the one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen.

[0028] In some embodiments, the pharmaceutical composition comprises one or more analgesic agent(s), individually or in combination, in an amount between 50-2000 mg, 50-1500 mg, 50-1200 mg, 50-1000 mg, 50-800 mg, 50-600 mg, 50-500 mg, 50-400 mg, 50-300 mg, 50-250 mg, 50-200 mg, 50-100 mg, 100-2000 mg, 100-1500 mg, 100-1200 mg, 100-1000 mg, 100-800 mg, 100-600 mg, 100-500 mg, 100-400 mg, 100-300 mg, 100-200 mg, 200-2000 mg, 200-1500 mg, 200-1200 mg, 200-1000 mg, 200-800 mg, 200-600 mg, 200-400 mg, 400-2000 mg, 400-1500 mg, 400-1200 mg, 400-1000 mg, 400-800 mg, 400-600 mg, 600-2000 mg, 600-1500 mg, 600-1200 mg, 600-1000 mg, 600-800 mg, 800-2000 mg, 800-1500 mg, 800-1200 mg, 800-1000 mg, 1000-2000 mg, 1000-1500 mg, 1000-1200 mg, 1200-2000 mg, 1200-1500 mg or 1500-2000 mg; and one or more α-blockers in an amount between 0.01-100 mg, 0.01-30 mg, 0.01-10 mg, 0.01-3 mg, 0.01-1 mg, 0.01-0.3 mg, 0.01-0.1

mg, 0.01-0.03 mg, 0.03-100 mg, 0.03-30 mg, 0.03-10 mg, 0.03-3 mg, 0.03-1 mg, 0.03-0.3 mg, 0.03-0.1 mg, 0.1-100 mg, 0.1-30 mg, 0.1-10 mg, 0.1-3 mg, 0.1-1 mg, 0.1-0.3 mg, 0.3-100 mg, 0.3-30 mg, 0.3-10 mg, 0.3-3 mg, 0.3-1 mg and 0.2-1 mg.

[0029] In some embodiments, the α-blocker is a non-selective α-blocker. In other embodiments, the α-blocker is a selective α1-adrenergic blocker. In other embodiments, the α-blocker is a selective α2-adrenergic blocker. In other embodiments, the α-blocker is tamsulosin.

[0030] In some embodiments, the pharmaceutical composition comprises acetaminophen in an amount between 100-200 mg, 200-400 mg, 400-600 mg, 600-800 mg, 800-1000 mg, or 1000-1200 mg and tamsulosin in an amount between 0.1-0.3 mg, 0.3-0.6 mg, 0.6-0.9 mg, 0.9-1.2 mg or 1.2-1.5 mg.

[0031] In other embodiments, both the one or more analgesic agents and the one or more α-blockers are formulated for immediate release. In other embodiments, the one or more analgesic agents are formulated for immediate release and the one or more α-blockers are formulated for extended release.

[0032] In other embodiments, the one or more analgesic agents are formulated for extended release and the one or more α-blockers are formulated for immediate release. In some embodiments, the one or more analgesic agents are released continuously, or at a steady rate, over a period or 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours. In some embodiments, at least 90% of the one or more analgesic agents are released continuously, or at a steady rate, over a period or 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0033] In some other embodiments, the one or more analgesic agents are released within 2 hours of administration and the remainder are released continuously, or at a steady rate, over a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0034] In other embodiments, both the one or more analgesic agents and the one or more α-blockers are formulated for extended release. In some embodiments, both the one or more analgesic agents and the one or more α-blockers are formulated for extended release such that the one or more analgesic agents and the one or more α-blockers are released continuously, or at a steady rate, over a period or 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours. In some other embodiments, both the one or more analgesic agents and the one or more α-blockers are formulated for extended release with a two-phase release profile in which 20-60% of the that the one or more analgesic agents and the one or more α-blockers are released within 2 hours of administration and the remainder are released continuously, or at a steady rate, over a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0035] In some embodiments, the pharmaceutical composition comprises acetaminophen in amount between 50-1000 mg, 50-250 mg, 250-400 mg, 400-600 mg, 600-800 mg or 800-1000 mg in combination with tamsulosin in an amount between 0.1-1.2 mg, 0.1-0.3 mg, 0.3-0.6 mg, 0.6-0.9 mg or 0.9-1.2 mg, wherein the composition is formulated for extended release of both acetaminophen and tamsulosin with a drug release profile in which at least 90% of the acetaminophen and tamsulosin is released, continuously, or at a steady rate, over a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0036] In other embodiments, the pharmaceutical composition comprises acetaminophen in an amount between 500-1000 mg, 50-200 mg, 50-400 mg, 100-400 mg, 100-300 mg, 200-400 mg, 400-600 mg, 600-800 mg, 800-1000 mg, or 1000-1200 mg and tamsulosin in an amount between 0.1-1.2 mg, 0.1-0.3 mg, 0.3-0.6 mg, 0.6-0.9 mg or 0.9-1.2 mg, wherein the composition is formulated for extended release with a two-phase release profile in which 20-60% of the acetaminophen and tamsulosin are released within 2 hours of administration, and the remainder are released, continuously, or at a steady rate, in a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0037] "Extended-release," also known as sustained-release (SR), sustained-action (SA), time-release (TR), controlled-release (CR), modified release (MR), or continuous-release (CR), is a mechanism used in medicine tablets or capsules to dissolve slowly and release the active ingredient over time. The advantages of extended-release tablets or capsules are that they can often be taken less frequently than immediate-release formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream, thus extending the duration of the drug action and lowering the peak amount of drug in the bloodstream. For example, an extended-release analgesic may allow a person to sleep through the night without getting up for the bathroom.

[0038] In one embodiment, the pharmaceutical composition is formulated for extended-release by embedding the active ingredient in a matrix of insoluble substance(s) such as acrylics or chitin. An extended-release form is designed to release the analgesic compound at a predetermined rate by maintaining a constant drug level for a specific period of time. This can be achieved through a variety of formulations, including, but not limited to, liposomes and drug-polymer conjugates, such as hydrogels.

[0039] An extended-release formulation can be designed to release the active agents at a predetermined rate so as to maintain a constant drug level for a specified, extended period of time, such as up to about 24 hours, about 20 hours, about 16 hours, about 12 hours, about 10 hours, about 9 hours, about 8 hours, about 7 hours, about 6 hours, about 5 hours,

about 4 hours, about 3 hours, about 2 hours, or about 1 hour following administration or following a lag period associated with delayed-release of the drug.

[0040] In certain preferred embodiments, the active agents are released over a time interval of between about 2 to about 10 hours. Alternatively, the active agents may be released over about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9, about 10 hours, about 12 hours, about 16 hours, about 20 hours or about 24 hours. In yet other embodiments, the active agents are released over a time period between about three to about eight hours following administration.

[0041] In some embodiments, the extended-release formulation comprises an active core comprised of one or more inert particles, each in the form of a bead, pellet, pill, granular particle, microcapsule, microsphere, microgranule, nanocapsule, or nanosphere coated on its surfaces with drugs in the form of *e.g.*, a drug-containing coating or film-forming composition using, for example, fluid bed techniques or other methodologies known to those of skill in the art. The inert particle can be of various sizes, so long as it is large enough to remain poorly dissolved. Alternatively, the active core may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer composition containing the drug substance.

[0042] The active agents may be introduced to the inert carrier by techniques known to one skilled in the art, such as drug layering, powder coating, extrusion/spheronization, roller compaction or granulation. The amount of drug in the core will depend on the dose that is required, and typically varies from about 5 to 90 weight %. Generally, the polymeric coating on the active core will be from about 1 to 50% based on the weight of the coated particle, depending on the lag time required and/or the polymers and coating solvents chosen. Those skilled in the art will be able to select an appropriate amount of drug for coating onto or incorporating into the core to achieve the desired dosage. In one embodiment, the inactive core may be a sugar sphere or a buffer crystal or an encapsulated buffer crystal such as calcium carbonate, sodium bicarbonate, fumaric acid, tartaric acid, etc. which alters the microenvironment of the drug to facilitate its release.

[0043] Another aspect of the present application relates to a method for reducing the frequency of urination. The method comprises administering to a subject in need thereof an effective amount of one or more analgesic agents, and an effective amount of a 5α-reductase inhibitor. Examples of 5α-reductase inhibitors include, but are not limited to, finasteride, bexlosteride, epristeride, izonsteride , lapisteride and turosteride. In some embodiments, the 5α-reductase inhibitor is finasteride.

[0044] In some embodiments, the one or more analgesic agents and the 5α-reductase inhibitor are administered separately in different dosage forms. In other embodiments, the one or more analgesic agents and the α-blocker are administered simultaneously in a single dosage form (e.g., in a single pill or tablet). In some embodiments, both the one or more analgesic agents and the 5α-reductase inhibitor are formulated for immediate release after administration. In other embodiments, both the one or more analgesic agents and the 5α-reductase inhibitor are formulated for delayed- release after administration. In other embodiments, both the one or more analgesic agents and the 5α-reductase inhibitor are formulated for extended release after administration. In other embodiments, both the one or more analgesic agents and the 5α-reductase inhibitor are formulated for delayed-extended release after administration. In other embodiments, the one or more analgesic agents are formulated for delayed-release, extended release or delayed extended release, and the 5α-reductase inhibitor is formulated for immediate release. In yet other embodiments, the one or more analgesic agents are formulated for immediate release, and the 5α-reductase inhibitor is formulated for delayed-release, extended release or delayed extended release. The method can be used for the treatment of nocturia or overactive bladder. Another aspect of the present application relates to a pharmaceutical composition comprising an active ingredient comprising one or more analgesic agents, a 5α-reductase inhibitor, and a pharmaceutically acceptable carrier.

[0045] In some embodiments, the one or more analgesic agents are administered orally in an individual or combined daily dose of 50-2000 mg, 50-1500 mg, 50-1200 mg, 50-1000 mg, 50-800 mg, 50-600 mg, 50-500 mg, 50-400 mg, 50-300 mg, 50-250 mg, 50-200 mg, 50-100 mg, 100-2000 mg, 100-1500 mg, 100-1200 mg, 100-1000 mg, 100-800 mg, 100-600 mg, 100-500 mg, 100-400 mg, 100-300 mg, 100-200 mg, 200-2000 mg, 200-1500 mg, 200-1200 mg, 200-1000 mg, 200-800 mg, 200-600 mg, 200-400 mg, 400-2000 mg, 400-1500 mg, 400-1200 mg, 400-1000 mg, 400-800 mg, 400-600 mg, 600-2000 mg, 600-1500 mg, 600-1200 mg, 600-1000 mg, 600-800 mg, 800-2000 mg, 800-1500 mg, 800-1200 mg, 800-1000 mg, 1000-2000 mg, 1000-1500 mg, 1000-1200 mg, 1200-2000 mg, 1200-1500 mg or 1500-2000 mg; and the one or more 5α-reductase inhibitors are administered orally in an individual or combined daily dose of between 0.1-250 mg, 0.1-100 mg, 0.1-30 mg, 0.1-10 mg, 0.1-3 mg, 0.1-1 mg, 0.3-250 mg, 0.3-100 mg, 0.3-30 mg, 0.3-10 mg, 0.3-3 mg, 0.3-1 mg, 1-100 mg, 1-30 mg, 1-10 mg, 1-3 mg, 3-7 mg and 4-6 mg.

[0046] In some embodiments, the 5α-reductase inhibitor is tamsulosin.

[0047] Another aspect of the present application relates to a pharmaceutical composition comprising: one or more analgesic agents; one or more 5α-reductase inhibitors; and a pharmaceutically acceptable carrier. In some embodiments, the one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen.

[0048] In some embodiments, the pharmaceutical composition comprises one or more analgesic agent(s), individually or in combination, in an amount between 50-2000 mg, 50-1500 mg, 50-1200 mg, 50-1000 mg, 50-800 mg, 50-600 mg, 50-500 mg, 50-400 mg, 50-300 mg, 50-250 mg, 50-200 mg, 50-100 mg, 100-2000 mg, 100-1500 mg, 100-1200 mg, 100-1000 mg, 100-800 mg, 100-600 mg, 100-500 mg, 100-400 mg, 100-300 mg, 100-200 mg, 200-2000 mg, 200-1500 mg, 200-1200 mg, 200-1000 mg, 200-800 mg, 200-600 mg, 200-400 mg, 400-2000 mg, 400-1500 mg, 400-1200 mg, 400-1000 mg, 400-800 mg, 400-600 mg, 600-2000 mg, 600-1500 mg, 600-1200 mg, 600-1000 mg, 600-800 mg, 800-2000 mg, 800-1500 mg, 800-1200 mg, 800-1000 mg, 1000-2000 mg, 1000-1500 mg, 1000-1200 mg, 1200-2000 mg, 1200-1500 mg or 1500-2000 mg; and one or more 5α-reductase inhibitor in an amount between 0.1-250 mg, 0.1-100 mg, 0.1-30 mg, 0.1-10 mg, 0.1-3 mg, 0.1-1 mg, 0.3-250 mg, 0.3-100 mg, 0.3-30 mg, 0.3-10 mg, 0.3-3 mg, 0.3-1 mg, 1-100 mg, 1-30 mg, 1-10 mg, 1-3 mg, 3-7 mg and 4-6 mg.

[0049] In some embodiments, the α-blocker is a non-selective α-blocker. In other embodiments, the α-blocker is a selective α1-adrenergic blocker. In other embodiments, the α-blocker is a selective α2-adrenergic blocker. In other embodiments, the α-blocker is tamsulosin.

[0050] In some embodiments, the pharmaceutical composition comprises acetaminophen in an amount between 100-200 mg, 200-400 mg, 400-600 mg, 600-800 mg, 800-1000 mg, or 1000-1200 mg and finasteride in an amount between 0.1-0.3 mg, 0.3-0.6 mg, 0.6-0.9 mg, 0.9-1.2 mg or 1.2-1.5 mg.

[0051] In other embodiments, both the one or more analgesic agents and the one or more 5α-reductase inhibitors are formulated for immediate release. In other embodiments, the one or more analgesic agents are formulated for immediate release and the one or more α-blockers are formulated for extended release.

[0052] In other embodiments, the one or more analgesic agents are formulated for extended release and the one or more 5α-reductase inhibitors are formulated for immediate release. In some embodiments, the one or more analgesic agents are released continuously, or at a steady rate, over a period or 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours. In some

embodiments, at least 90% of the one or more analgesic agents are released continuously, or at a steady rate, over a period or 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0053] In some other embodiments, the one or more analgesic agents are released within 2 hours of administration and the remainder are released continuously, or at a steady rate, over a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0054] In other embodiments, both the one or more analgesic agents and the one or more 5α-reductase inhibitors are formulated for extended release. In some embodiments, both the one or more analgesic agents and the one or more 5α-reductase inhibitors are formulated for extended release such that the one or more analgesic agents and the one or more 5α-reductase inhibitors are released continuously, or at a steady rate, over a period or 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours. In some other embodiments, both the one or more analgesic agents and the one or more 5α-reductase inhibitors are formulated for extended release with a two-phase release profile in which 20-60% of the that the one or more analgesic agents and the one or more 5α-reductase inhibitors are released within 2 hours of administration and the remainder are released continuously, or at a steady rate, over a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0055] In some embodiments, the pharmaceutical composition comprises acetaminophen in amount between 50-1000 mg, 50-250 mg, 250-400 mg, 400-600 mg, 600-800 mg or 800-1000 mg in combination with finasteride in an amount between 1-20 mg, 1-3 mg, 3-7 mg, 7-10 mg, 10-15 mg or 15-20 mg, wherein the composition is formulated for extended release of both acetaminophen and finasteride with a drug release profile in which at least 90% of the acetaminophen and finasteride is released, continuously, or at a steady rate, over a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0056] In other embodiments, the pharmaceutical composition comprises acetaminophen in an amount between 50-1000 mg, 50-100 mg, 50-200 mg, 50-300 mg, 50-400 mg, 50-600 mg, 50-800 mg, 100-200 mg, 100-300 mg, 100-400 mg, 100-600 mg, 100-800 mg, 100-1000 mg, 200-400 mg, 200-600 mg, 200-800 mg, 200-1000 mg, 400-600 mg, 400-800 mg, 400-1000 mg, 600-800 mg, 600-1000 mg, 800-1000 mg, or 1000-1200 mg and finasteride in an amount between 1-20 mg, 1-3 mg, 1-7 mg, 1-10 mg, 1-15 mg, 3-7 mg, 3-10 mg, 3-15 mg, 3-20 mg, 7-10 mg, 7-15 mg, 7-20 mg, 10-15 mg, 10-20 mg or 15-20 mg, wherein the composition is formulated for extended release with a two-phase release profile in which 20-60% of the acetaminophen and finasteride are released within 2 hours of administration, and the remainder are released, continuously, or at a steady rate, in a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0057] "Extended-release," also known as sustained-release (SR), sustained-action (SA), time-release (TR), controlled-release (CR), modified release (MR), or continuous-release (CR), is a mechanism used in medicine tablets or capsules to dissolve slowly and release the active ingredient over time. The advantages of extended-release tablets or capsules are that they can often be taken less frequently than immediate-release formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream, thus extending the duration of the drug action and lowering the peak amount of drug in the bloodstream. For example, an extended-release analgesic may allow a person to sleep through the night without getting up for the bathroom.

[0058] In one embodiment, the pharmaceutical composition is formulated for extended-release by embedding the active ingredient in a matrix of insoluble substance(s) such as acrylics or chitin. An extended-release form is designed to release the analgesic compound at a predetermined rate by maintaining a constant drug level for a specific period of time. This can be achieved through a variety of formulations, including, but not limited to, liposomes and drug-polymer conjugates, such as hydrogels.

[0059] An extended-release formulation can be designed to release the active agents at a predetermined rate so as to maintain a constant drug level for a specified, extended period of time, such as up to about 24 hours, about 20 hours, about 16 hours, about 12 hours, about 10 hours, about 9 hours, about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, or about 1 hour following administration or following a lag period associated with delayed-release of the drug.

[0060] In certain preferred embodiments, the active agents are released over a time interval of between about 2 to about 10 hours. Alternatively, the active agents may be released over about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9, about 10 hours, about 12 hours, about 16 hours, about 20 hours or about 24 hours. In yet other embodiments, the active agents are released over a time period between about three to about eight hours following administration.

[0061] In some embodiments, the extended-release formulation comprises an active core comprised of one or more inert particles, each in the form of a bead, pellet, pill, granular particle, microcapsule, microsphere, microgranule, nanocapsule, or nanosphere coated on its surfaces with drugs in the form of *e.g.*, a drug-containing coating or film-forming composition using, for example, fluid bed techniques or other methodologies known to those of skill in the art. The inert particle can be of various sizes, so long as it is large enough to remain poorly dissolved. Alternatively, the active core may be prepared by granulating and

milling and/or by extrusion and spheronization of a polymer composition containing the drug substance.

[0001] The active agents may be introduced to the inert carrier by techniques known to one skilled in the art, such as drug layering, powder coating, extrusion/spheronization, roller compaction or granulation. The amount of drug in the core will depend on the dose that is required, and typically varies from about 5 to 90 weight %. Generally, the polymeric coating on the active core will be from about 1 to 50% based on the weight of the coated particle, depending on the lag time required and/or the polymers and coating solvents chosen. Those skilled in the art will be able to select an appropriate amount of drug for coating onto or incorporating into the core to achieve the desired dosage. In one embodiment, the inactive core may be a sugar sphere or a buffer crystal or an encapsulated buffer crystal such as calcium carbonate, sodium bicarbonate, fumaric acid, tartaric acid, etc. which alters the microenvironment of the drug to facilitate its release.

[0062] Extended-release formulations may utilize a variety of extended-release coatings or mechanisms facilitating the gradual release of active agents over time. In some embodiments, the extended-release agent comprises a polymer controlling release by dissolution controlled release. In a particular embodiment, the active agent(s) are incorporated in a matrix comprising an insoluble polymer and drug particles or granules coated with polymeric materials of varying thickness. The polymeric material may comprise a lipid barrier comprising a waxy material, such as carnauba wax, beeswax, spermaceti wax, candellila wax, shallac wax, cocoa butter, cetostearyl alcohol, partially hydrogenated vegetable oils, ceresin, paraffin wax, ceresine, myristyl alcohol, stearyl alcohol, cetyl alcohol and stearic acid, along with surfactants, such as polyoxyethylene sorbitan monooleate. When contacted with an aqueous medium, such as biological fluids, the polymer coating emulsifies or erodes after a predetermined lag-time depending on the thickness of the polymer coating. The lag time is independent of gastrointestinal motility, pH, or gastric residence.

[0063] In other embodiments, the extended-release agent comprises a polymeric matrix effecting diffusion controlled release. The matrix may comprise one or more hydrophilic and/or water-swellable, matrix forming polymers, pH-dependent polymers, and/or pH-independent polymers.

[0064] In one embodiment, the extended-release formulation comprises a water soluble or water-swellable matrix-forming polymer, optionally containing one or more solubility-enhancing excipients and/or release-promoting agents. Upon solubilization of the water soluble polymer, the active agent(s) dissolve (if soluble) and gradually diffuse through

the hydrated portion of the matrix. The gel layer grows with time as more water permeates into the core of the matrix, increasing the thickness of the gel layer and providing a diffusion barrier to drug release. As the outer layer becomes fully hydrated, the polymer chains become completely relaxed and can no longer maintain the integrity of the gel layer, leading to disentanglement and erosion of the outer hydrated polymer on the surface of the matrix. Water continues to penetrate towards the core through the gel layer, until it has been completely eroded. Whereas soluble drugs are released by this combination of diffusion and erosion mechanisms, erosion is the predominant mechanism for insoluble drugs, regardless of dose.

[0065] Similarly, water-swellable polymers typically hydrate and swell in biological fluids forming a homogenous matrix structure that maintains its shape during drug release and serves as a carrier for the drug, solubility enhancers and/or release promoters. The initial matrix polymer hydration phase results in slow-release of the drug (lag phase). Once the water swellable polymer is fully hydrated and swollen, water within the matrix can similarly dissolve the drug substance and allow for its diffusion out through the matrix coating.

[0066] Additionally, the porosity of the matrix can be increased due to the leaching out of pH-dependent release promoters so as to release the drug at a faster rate. The rate of the drug release then becomes constant and is a function of drug diffusion through the hydrated polymer gel. The release rate from the matrix is dependent upon various factors, including polymer type and level; drug solubility and dose; polymer: drug ratio; filler type and level; polymer to filler ratio; particle size of drug and polymer; and porosity and shape of the matrix.

[0067] Exemplary hydrophilic and/or water-swellable, matrix forming polymers include, but are not limited to, cellulosic polymers, including hydroxyalkyl celluloses and carboxyalkyl celluloses, such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), methylcellulose (MC), carboxymethylcellulose (CMC), powdered cellulose such as microcrystalline cellulose, cellulose acetate, ethylcellulose, salts thereof, and combinations thereof; alginates, gums, including heteropolysaccharide gums and homopolysaccharide gums, such as xanthan, tragacanth, pectin, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, veegum, carrageenan, locust bean gum, gellan gum, and derivatives thereofrom; acrylic resins, including polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate and cross-linked polyacrylic acid derivatives such as Carbomers (*e.g.*, CARBOPOL®, such as including CARBOPOL® 71G NF, available in various molecular

weight grades from Noveon, Inc., Cincinnati, OH); carageenan; polyvinyl acetate (*e.g.,* KOLLIDON® SR); polyvinyl pyrrolidone and its derivatives such as crospovidone; polyethylene oxides; and polyvinyl alcohol. Preferred hydrophilic and water-swellable polymers include the cellulosic polymers, especially HPMC.

[0068] The extended-release formulation may further comprise at least one binder that is capable of cross-linking the hydrophilic compound to form a hydrophilic polymer matrix (*i.e.*, a gel matrix) in an aqueous medium, including biological fluids.

[0069] Exemplary binders include homopolysaccharides, such as galactomannan gums, guar gum, hydroxypropyl guar gum, hydroxypropylcellulose (HPC; *e.g.*, Klucel EXF) and locust bean gum. In other embodiments, the binder is an alginic acid derivative, HPC or microcrystallized cellulose (MCC). Other binders include, but are not limited to, starches, microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose and polyvinylpyrrolidone.

[0070] In one embodiment, the introduction method is drug layering by spraying a suspension of active agent(s) and a binder onto the inert carrier.

[0071] The binder may be present in the bead formulation in an amount of from about 0.1% to about 15% by weight, and preferably of from about 0.2% to about 10% by weight.

[0072] In some embodiments, the hydrophilic polymer matrix may further include an ionic polymer, a non-ionic polymer, or water-insoluble hydrophobic polymer to provide a stronger gel layer and/or reduce pore quantity and dimensions in the matrix so as to slow diffusion and erosion rates and concomitant release of the active agent(s). This may additionally suppress the initial burst effect and produce a more steady, "zero order release" of active agent(s).

[0073] Exemplary ionic polymers for slowing dissolution rate include both anionic and cationic polymers. Exemplary anionic polymers include, for example, sodium carboxymethylcellulose (Na CMC), sodium alginate, polymers of acrylic acid or carbomers (*e.g.,* CARBOPOL® 934, 940, 974P NF); enteric polymers, such as polyvinyl acetate phthalate (PVAP), methacrylic acid copolymers (*e.g.*, EUDRAGIT® L100, L 30D 55, A, and FS 30D), hypromellose acetate succinate (AQUAT HPMCAS); and xanthan gum. Exemplary cationic polymers include, for example, dimethylaminoethyl methacrylate copolymer (*e.g.*, EUDRAGIT® E 100). Incorporation of anionic polymers, particularly enteric polymers, is useful for developing a pH-independent release profile for weakly basic drugs as compared to hydrophilic polymer alone.

[0074] Exemplary non-ionic polymers for slowing dissolution rate, include, for example, hydroxypropylcellulose (HPC) and polyethylene oxide (PEO) (*e.g.*, POLYOX™)

[0075] Exemplary hydrophobic polymers include ethylcellulose (*e.g.*, ETHOCEL™, SURELEASE®), cellulose acetate, methacrylic acid copolymers (*e.g.*, EUDRAGIT® NE 30D), ammonio-methacrylate copolymers (*e.g.*, EUDRAGIT® RL 100 or PO RS100), polyvinyl acetate, glyceryl monostearate, fatty acids, such as acetyl tributyl citrate, and combinations and derivatives thereof.

[0076] The swellable polymer can be incorporated in the formulation in proportion from 1% to 50% by weight, preferably from 5% to 40% by weight, most preferably from 5% to 20% by weight. The swellable polymers and binders may be incorporated in the formulation either prior to or after granulation. The polymers can also be dispersed in organic solvents or hydro-alcohols and sprayed during granulation.

[0077] Exemplary release-promoting agents include pH-dependent enteric polymers that remain intact at pH value lower than about 4.0 and dissolve at pH values higher than 4.0, preferably higher than 5.0, most preferably about 6.0, are considered useful as release-promoting agents for this invention. Exemplary pH-dependent polymers include, but are not limited to, methacarylic acid copolymers, methacrylic acid-methyl methacrylate copolymers (*e.g.,* EUDRAGIT® L100 (Type A), EUDRAGIT® S100 (Type B), Rohm GmbH, Germany; methacrylic acid-ethyl acrylate copolymers (*e.g.*, EUDRAGIT® L100-55 (Type C) and EUDRAGIT® L30D-55 copolymer dispersion, Rohm GmbH, Germany); copolymers of methacrylic acid-methyl methacrylate and methyl methacrylate (EUDRAGIT® FS); terpolymers of methacrylic acid, methacrylate, and ethyl acrylate; cellulose acetate phthalates (CAP); hydroxypropyl methylcellulose phthalate (HPMCP) (*e.g.*, HP-55, HP-50, HP-55S, Shinetsu Chemical, Japan); polyvinyl acetate phthalates (PVAP) (*e.g.*, COATERIC®, OPADRY® enteric white OY-P-7171); polyvinylbutyrate acetate; cellulose acetate succinates (CAS); hydroxypropyl methylcellulose acetate succinate (HPMCAS), *e.g.*, HPMCAS LF Grade, MF Grade, HF Grade, including AQOAT® LF and AQOAT® MF (Shin-Etsu Chemical, Japan); Shinetsu Chemical, Japan); shellac (*e.g.*, MARCOAT™ 125 & MARCOAT™ 125N); vinyl acetate-maleic anhydride copolymer; styrene-maleic monoester copolymer; carboxymethyl ethylcellulose (CMEC, Freund Corporation, Japan); cellulose acetate phthalates (CAP) (*e.g.*, AQUATERIC®); cellulose acetate trimellitates (CAT); and mixtures of two or more thereof at weight ratios between about 2:1 to about 5:1, such as, for instance, a mixture of EUDRAGIT® L 100-55 and EUDRAGIT® S 100 at a weight ratio of

about 3:1 to about 2:1, or a mixture of EUDRAGIT® L 30 D-55 and EUDRAGIT® FS at a weight ratio of about 3:1 to about 5:1.

[0078] These polymers may be used either alone or in combination, or together with polymers other than those mentioned above. Preferred enteric pH-dependent polymers are the pharmaceutically acceptable methacrylic acid copolymers. These copolymers are anionic polymers based on methacrylic acid and methyl methacrylate and, preferably, have a mean molecular weight of about 135,000. A ratio of free carboxyl groups to methyl-esterified carboxyl groups in these copolymers may range, for example, from 1:1 to 1:3, *e.g.* around 1:1 or 1:2. Such polymers are sold under the trade name Eudragit® such as the Eudragit L series *e.g.*, Eudragit L 12.5®, Eudragit L 12.5P®, Eudragit L100®, Eudragit L 100-55®, Eudragit L-30D®, Eudragit L-30 D-55®, the Eudragit S® series *e.g.,* Eudragit S 12.5®, Eudragit S 12.5P®, Eudragit S100®. The release promoters are not limited to pH dependent polymers. Other hydrophilic molecules that dissolve rapidly and leach out of the dosage form quickly leaving a porous structure can be also be used for the same purpose.

[0079] The release-promoting agent can be incorporated in an amount from 10% to 90%, preferably from 20% to 80% and most preferably from 30% to 70% by weight of the dosage unit. The agent can be incorporated into the formulation either prior to or after granulation. The release-promoting agent can be added into the formulation either as a dry material, or it can be dispersed or dissolved in an appropriate solvent, and dispersed during granulation.

[0080] In some embodiments, the matrix may include a combination of release promoters and solubility enhancers. The solubility enhancers can be ionic and non-ionic surfactants, complexing agents, hydrophilic polymers, pH modifiers, such as acidifying agents and alkalinizing agents, as well as molecules that increase the solubility of poorly soluble drug through molecular entrapment. Several solubility enhancers can be utilized simultaneously.

[0081] Solubility enhancers may include surface active agents, such as sodium docusate, sodium lauryl sulfate, sodium stearyl fumarate, Tweens® and Spans (PEO modified sorbitan monoesters and fatty acid sorbitan esters), poly(ethylene oxide)-polypropylene oxide-poly(ethylene oxide) block copolymers (aka PLURONICS™); complexing agents such as low molecular weight polyvinyl pyrrolidone and low molecular weight hydroxypropyl methyl cellulose; molecules that aid solubility by molecular entrapment such as cyclodextrins, and pH modifying agents, including acidifying agents such as citric acid,

fumaric acid, tartaric acid, and hydrochloric acid; and alkalizing agents such as meglumine and sodium hydroxide.

[0082] Solubility enhancing agents typically constitute from 1% to 80% by weight, preferably from 1% to 60%, more preferably from 1% to 50%, of the dosage form and can be incorporated in a variety of ways. They can be incorporated in the formulation prior to granulation in dry or wet form. They can also be added to the formulation after the rest of the materials are granulated or otherwise processed. During granulation, solubilizers can be sprayed as solutions with or without a binder.

[0083] In some embodiments, the extended-release formulation comprises a polymeric matrix that can provide for release of the drug after a certain time, independent of the pH. For purposes of the present invention, "pH independent" is defined as having characteristics (*e.g.*, dissolution) which are substantially unaffected by pH. pH independent polymers are often referred to in the context of "time-controlled" or "time-dependent" release profiles.

[0084] A pH independent polymer may be used to coat the active agent and/or provide a polymer for a hydrophilic matrix in the extended-release coating thereover. The pH independent polymer may be water-insoluble or water soluble. Exemplary water insoluble pH independent polymers include, but are not limited to, neutral methacrylic acid esters with a small portion of trimethylammonioethyl methacrylate chloride (*e.g.*, EUDRAGIT® RS and EUDRAGIT® RL; neutral ester dispersions without any functional groups (*e.g.*, EUDRAGIT® NE30D and EUDRAGIT® NE30); cellulosic polymers, such as ethylcellulose, hydroxyl ethyl cellulose, cellulose acetate or mixtures and other pH independent coating products. Exemplary water soluble pH independent polymers include hydroxyalkyl cellulose ethers, such as hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose (HPC); polyvinylpyrrolidone (PVP), methylcellulose, OPADRY®amb, guar gum, xanthan gum, gum arabic, hydroxyethyl cellulose and ethyl acrylate and methyl methacrylate copolymer dispersion or combinations thereof.

[0085] In one embodiment, the extended-release formulation comprises a water-insoluble water-permeable polymeric coating or matrix comprising one or more water-insoluble water-permeable film-forming over the active core. The coating may additionally include one or more water soluble polymers and/or one or more plasticizers. The water-insoluble polymer coating comprises a barrier coating for release of active agents in the core, wherein lower molecular weight (viscosity) grades exhibit faster release rates as compared to higher viscosity grades.

[0086] In preferred embodiments, the water-insoluble film-forming polymers include one or more alkyl cellulose ethers, such as ethyl celluloses and mixtures thereof, (*e.g.*, ethyl cellulose grades PR100, PR45, PR20, PR10 and PR7; ETHOCEL®, Dow).

[0087] An exemplary water-soluble polymer such as polyvinylpyrrolidone (POVIDONE®), hydroxypropyl methylcellulose, hydroxypropyl cellulose and mixtures thereof.

[0088] In some embodiments, the water-insoluble polymer provides suitable properties (*e.g.,* extended-release characteristics, mechanical properties, and coating properties) without the need for a plasticizer. For example, coatings comprising polyvinyl acetate (PVA), neutral copolymers of acrylate/methacrylate esters such as commercially available Eudragit NE30D from Evonik Industries, ethyl cellulose in combination with hydroxypropylcellulose, waxes, etc. can be applied without plasticizers.

[0089] In yet another embodiment, the water-insoluble polymer matrix may further include a plasticizer. The amount of plasticizer required depends upon the plasticizer, the properties of the water-insoluble polymer, and the ultimate desired properties of the coating. Suitable levels of plasticizer range from about 1% to about 20%, from about 3% to about 20%, about 3% to about 5%, about 7% to about 10%, about 12% to about 15%, about 17% to about 20%, or about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, or about 20% by weight relative to the total weight of the coating, inclusive of all ranges and sub-ranges therebetween.

[0090] Exemplary plasticizers include, but are not limited to, triacetin, acetylated monoglyceride, oils (castor oil, hydrogenated castor oil, rape seed oil, sesame oil, olive oil, etc.); citrate esters, triethyl citrate, acetyltriethyl citrate acetyltributyl citrate, tributyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl phthalate, dioctyl phthalate, methyl paraben, propyl paraben, propyl paraben, butyl paraben, diethyl sebacate, dibutyl sebacate, glyceroltributyrate, substituted triglycerides and glycerides, monoacetylated and diacetylated glycerides (*e.g.*, MYVACET® 9-45), glyceryl monostearate, glycerol tributyrate, polysorbate 80, polyethyleneglycol (such as PEG-4000, PEG-400), propyleneglycol, 1,2-propyleneglycol, glycerin, sorbitol, diethyl oxalate, diethyl malate, diethyl fumarate, diethylmalonate, dibutyl succinate, fatty acids, glycerin, sorbitol, diethyl oxalate, diethyl malate, diethyl maleate, diethyl fumarate, diethyl succinate, diethyl malonate, dioctyl phthalate, dibutyl sebacate, and mixtures thereof. The plasticizer can have surfactant properties, such that it can act as a release modifier. For example, non-ionic detergents such at Brij 58 (polyoxyethylene (20) cetyl ether), and the like, can be used.

[0091] Plasticizers can be high boiling point organic solvents used to impart flexibility to otherwise hard or brittle polymeric materials and can affect the release profile for the active agent(s). Plasticizers generally cause a reduction in the cohesive intermolecular forces along the polymer chains resulting in various changes in polymer properties including a reduction in tensile strength, and increase in elongation and a reduction in the glass transition or softening temperature of the polymer. The amount and choice of the plasticizer can affect the hardness of a tablet, for example, and can even affect its dissolution or disintegration characteristics, as well as its physical and chemical stability. Certain plasticizers can increase the elasticity and/or pliability of a coat, thereby decreasing the coat's brittleness.

[0092] In another embodiment, the extended-release formulation comprises a combination of at least two gel-forming polymers, including at least one non-ionic gel-forming polymer and/or at least one anionic gel-forming polymer. The gel formed by the combination of gel-forming polymers provides controlled release, such that when the formulation is ingested and comes into contact with the gastrointestinal fluids, the polymers nearest the surface hydrate to form a viscous gel layer. Because of the high viscosity, the viscous layer dissolves away only gradually, exposing the material below to the same process. The mass thus dissolves away slowly, thereby slowly releasing the active ingredient into the gastrointestinal fluids. The combination of at least two gel-forming polymers enables properties of the resultant gel, such as viscosity, to be manipulated in order to provide the desired release profile.

[0093] In a particular embodiment, the formulation comprises at least one non-ionic gel-forming polymer and at least one anionic gel-forming polymer. In another embodiment, the formulation comprises two different non-ionic gel-forming polymers. In yet another embodiment, the formulation comprises a combination of non-ionic gel-forming polymers of the same chemistry, but having different solubilities, viscosities, and/or molecular weights (for example a combination of hydroxyproplyl methylcellulose of different viscosity grades, such as HPMC K100 and HPMC K15M or HPMC K100M).

[0094] Exemplary anionic gel forming polymers include, but are not limited to, sodium carboxymethylcellulose (Na CMC), carboxymethyl cellulose (CMC), anionic polysaccharides such as sodium alginate, alginic acid, pectin, polyglucuronic acid (poly-α- and -β-1,4-glucuronic acid), polygalacturonic acid (pectic acid), chondroitin sulfate, carrageenan, furcellaran, anionic gums such as xanthan gum, polymers of acrylic acid or

carbomers (Carbopol® 934, 940, 974P NF), Carbopol® copolymers, a Pemulen® polymer, polycarbophil, and others.

[0095] Exemplary non-ionic gel-forming polymers include, but are not limited to, Povidone (PVP: polyvinyl pyrrolidone), polyvinyl alcohol, copolymer of PVP and polyvinyl acetate, HPC (hydroxypropyl cellulose), HPMC (hydroxypropyl methylcellulose), hydroxyethyl cellulose, hydroxymethyl cellulose, gelatin, polyethylene oxide, acacia, dextrin, starch, polyhydroxyethylmethacrylate (PHEMA), water soluble nonionic polymethacrylates and their copolymers, modified cellulose, modified polysaccharides, nonionic gums, nonionic polysaccharides and/or mixtures thereof.

[0096] The formulation may optionally comprise an enteric polymer as described above, and/or at least one excipient, such as a filler, a binder (as described above), a disintegrant, and/or a flow aid or glidant.

[0097] Exemplary fillers include but are not limited to, lactose, glucose, fructose, sucrose, dicalcium phosphate, sugar alcohols also known as "sugar polyol" such as sorbitol, manitol, lactitol, xylitol, isomalt, erythritol, and hydrogenated starch hydrolysates (a blend of several sugar alcohols), corn starch, potato starch, sodium carboxymethycellulose, ethylcellulose and cellulose acetate, enteric polymers, or a mixture thereof.

[0098] Exemplary binders, include but are not limited to, water-soluble hydrophilic polymers, such as Povidone (PVP: polyvinyl pyrrolidone), copovidone (a copolymer of polyvinyl pyrrolidone and polyvinyl acetate), low molecular weight HPC (hydroxypropyl cellulose) low molecular weight HPMC (hydroxypropyl methylcellulose), low molecular weight carboxy methyl cellulose, ethylcellulose, gelatin, polyethylene oxide, acacia, dextrin, magnesium aluminum silicate, starch, and polymethacrylates such as Eudragit NE 30D, Eudragit RL, Eudragit RS, Eudragit E, polyvinyl acetate, and enteric polymers, or mixtures thereof.

[0099] Exemplary disintegrants include but are not limited to low-substituted carboxymethyl cellulose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), sodium carboxymethyl starch (sodium starch glycolate), cross-linked sodium carboxymethyl cellulose (Croscarmellose), pregelatinized starch (starch 1500), microcrystalline cellulose, water insoluble starch, calcium carboxymethyl cellulose, low substituted hydroxypropyl cellulose, and magnesium or aluminum silicate.

[0100] Exemplary glidants include but are not limited to, magnesium, silicon dioxide, talc, starch, titanium dioxide, and the like.

[0101] In yet another embodiment, the extended-release formulation is formed by coating a water soluble/dispersible drug-containing particle, such as a bead or bead population therein (as described above), with a coating material, and, optionally, a pore former and other excipients. The coating material is preferably selected from a group comprising cellulosic polymers, such as ethylcellulose *(e.g.*, SURELEASE®), methylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, cellulose acetate, and cellulose acetate phthalate; polyvinyl alcohol; acrylic polymers such as polyacrylates, polymethacrylates and copolymers thereof, and other water-based or solvent-based coating materials. The release-controlling coating for a given bead population may be controlled by at least one parameter of the release controlling coating, such as the nature of the coating, coating level, type and concentration of a pore former, process parameters and combinations thereof. Thus, changing a parameter, such as a pore former concentration, or the conditions of the curing, allows for changes in the release of active agent(s) from any given bead population, thereby allowing for selective adjustment of the formulation to a pre-determined release profile.

[0102] Pore formers suitable for use in the release controlling coating herein can be organic or inorganic agents, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. Exemplary pore forming agents include, but are not limited to, organic compounds such as mono-, oligo-, and polysaccharides including sucrose, glucose, fructose, mannitol, mannose, galactose, sorbitol, pullulan, dextran; polymers soluble in the environment of use such as water-soluble hydrophilic polymers, hydroxyalkylcelluloses, carboxyalkylcelluloses, hydroxypropylmethylcellulose, cellulose ethers, acrylic resins, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, Carbowaxes, Carbopol, and the like, diols, polyols, polyhydric alcohols, polyalkylene glycols, polyethylene glycols, polypropylene glycols, or block polymers thereof, polyglycols, poly(α-Ω)alkylenediols; inorganic compounds such as alkali metal salts, lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, suitable calcium salts, combination thereof, and the like.

[0103] The release controlling coating can further comprise other additives known in the art, such as plasticizers, anti-adherents, glidants (or flow aids), and antifoams.

[0104] In some embodiments, the coated particles or beads may additionally include an "overcoat," to provide, *e.g.*, moisture protection, static charge reduction, taste-masking, flavoring, coloring, and/or polish or other cosmetic appeal to the beads. Suitable coating

materials for such an overcoat are known in the art, and include, but are not limited to, cellulosic polymers such as hydroxypropylmethylcellulose, hydroxypropylcellulose and microcrystalline cellulose, or combinations thereof (for example, various OPADRY® coating materials).

[0105] The coated particles or beads may additionally contain enhancers that may be exemplified by, but not limited to, solubility enhancers, dissolution enhancers, absorption enhancers, permeability enhancers, stabilizers, complexing agents, enzyme inhibitors, p-glycoprotein inhibitors, and multidrug resistance protein inhibitors. Alternatively, the formulation can also contain enhancers that are separated from the coated particles, for example in a separate population of beads or as a powder. In yet another embodiment, the enhancer(s) may be contained in a separate layer on coated particles either under or above the release controlling coating.

[0106] In other embodiments, the extended-release formulation is formulated to release the active agent(s) by an osmotic mechanism. By way of example, a capsule may be formulated with a single osmotic unit or it may incorporate 2, 3, 4, 5, or 6 push-pull units encapsulated within a hard gelatin capsule, whereby each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi-permeable membrane. One or more orifices are drilled through the membrane next to the drug layer. This membrane may be additionally covered with a pH-dependent enteric coating to prevent release until after gastric emptying. The gelatin capsule dissolves immediately after ingestion. As the push pull unit(s) enter the small intestine, the enteric coating breaks down, which then allows fluid to flow through the semi-permeable membrane, swelling the osmotic push compartment to force to force drugs out through the orifice(s) at a rate precisely controlled by the rate of water transport through the semi-permeable membrane. Release of drugs can occur over a constant rate for up to 24 hours or more.

[0107] The osmotic push layer comprises one or more osmotic agents creating the driving force for transport of water through the semi-permeable membrane into the core of the delivery vehicle. One class of osmotic agents includes water-swellable hydrophilic polymers, also referred to as "osmopolymers" and "hydrogels," including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate,

hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[0108] Another class of osmotic agents includes osmogens, which are capable of imbibing water to effect an osmotic pressure gradient across the semi-permeable membrane. Exemplary osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[0109] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking.

[0110] In some embodiments, the extended-release formulation may comprise a polysaccharide coating that is resistant to erosion in both the stomach and intestine. Such polymers can be only degraded in the colon, which contains a large microflora containing biodegradable enzymes breaking down, for example, the polysaccharide coatings to release the drug contents in a controlled, time-dependent manner. Exemplary polysaccharide coatings may include, for example, amylose, arabinogalactan, chitosan, chondroitin sulfate, cyclodextrin, dextran, guar gum, pectin, xylan, and combinations or derivatives therefrom.

[0111] In some embodiments, the pharmaceutical composition of the present application is formulated for delayed extended-release. As used herein, the term "delayed-release" refers to a medication that does not immediately disintegrate and release the active ingredient(s) into the body. In some embodiments, the term "delayed extended-release" is used with reference to a drug formulation having a release profile in which there is a predetermined delay in the release of the drug following administration. In some embodiments, the delayed extended-release formulation includes an extended-release formulation coated with an enteric coating, which is a barrier applied to oral medication that prevents release of medication before it reaches the small intestine. Delayed-release

formulations, such as enteric coatings, prevent drugs having an irritant effect on the stomach, such as aspirin, from dissolving in the stomach. Such coatings are also used to protect acid-unstable drugs from the stomach's acidic exposure, delivering them instead to a basic pH environment (intestine's pH 5.5 and above) where they do not degrade, and give their desired action.

[0112] The term "pulsatile release" is a type of delayed-release, which is used herein with reference to a drug formulation that provides rapid and transient release of the drug within a short time period immediately after a predetermined lag period, thereby producing a "pulsed" plasma profile of the drug after drug administration. Formulations may be designed to provide a single pulsatile release or multiple pulsatile releases at predetermined time intervals following administration, or a pulsatile release (e.g., 20-60% of the active ingredient) followed with extended release over a period of time (e.g., a continuous release of the remainder of the active ingredient).

[0113] A delayed-release or pulsatile release formulation generally comprises one or more elements covered with a barrier coating, which dissolves, erodes or ruptures following a specified lag phase. In some embodiments, the pharmaceutical composition of the present application is formulated for extended-release or delayed extended-release and comprises 100% of the total dosage of a given active agent administered in a single unit dose. In other embodiments, the pharmaceutical composition comprises an extended/delayed-release component and an immediate-release component. In some embodiments, the immediate-release component and the extended/delayed-release component contain the same active ingredient. In other embodiments, the immediate-release component and the extended/delayed-release component contain different active ingredients (*e.g.*, an analgesic in one component and an α-blocker in another component). In some embodiments, the first and second components each comprises an α-blocker and an analgesic selected from the group consisting of aspirin, ibuprofen, naproxen sodium, indomethacin, nabumetone, and acetaminophen. In other embodiments, the first and second components each comprises a 5α-reductase inhibitor selected from the group consisting of finasteride, bexlosteride, epristeride, izonsteride , lapisteride and turosteride, and an analgesic selected from the group consisting of aspirin, ibuprofen, naproxen sodium, indomethacin, nabumetone, and acetaminophen. In other embodiments, the extended/delayed-release component is coated with an enteric coating. In other embodiments, the immediate-release component and/or the extended/delayed-release component further comprises an antimuscarinic agent selected from the group consisting of oxybutynin, solifenacin, darifenacin and atropine. In other

embodiments, the immediate-release component and/or the extended/delayed-release component further comprises an antidiuretic agent, an antimuscarinic agent or both. In other embodiments, the treatment method includes administering to a subject a diuretic at least 8 or 7 hours prior to a target time, such as bedtime, and administering to the subject the pharmaceutical composition comprising the immediate-release component and/or the extended/delayed-release component within 2 hours prior to the target time.

[0114] In other embodiments, the "immediate-release" component provide about 5-50% of the total dosage of the active agent(s) and the "extended-release" component provides 50-95% of the total dosage of the active agent(s) to be delivered by the pharmaceutical formulation. For example, the immediate-release component may provide about 20-60%, or about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60% of the total dosage of the active agent(s) to be delivered by the pharmaceutical formulation. The extended-release component provides about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% of the total dosage of the active agent(s) to be delivered by the formulation. In some embodiments, the extended-release component further comprises a barrier coating to delay the release of the active agent.

[0115] A barrier coating for delayed-release may consist of a variety of different materials, depending on the objective. In addition, a formulation may comprise a plurality of barrier coatings to facilitate release in a temporal manner. The coating may be a sugar coating, a film coating (*e.g.*, based on hydroxypropyl methylcellulose, methylcellulose, methyl hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, acrylate copolymers, polyethylene glycols and/or polyvinylpyrrolidone), or a coating based on methacrylic acid copolymer, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, and/or ethylcellulose. Furthermore, the formulation may additionally include a time delay material such as, for example, glyceryl monostearate or glyceryl distearate.

[0116] In some embodiments, the delayed, extended-release formulation includes an enteric coating comprised one or more polymers facilitating release of active agents in proximal or distal regions of the gastrointestinal tract. As used herein, the term "enteric polymer coating" is a coating comprising of one or more polymers having a pH dependent or pH-independent release profile. Typically the coating resists dissolution in the acidic medium of the stomach, but dissolves or erodes in more distal regions of the gastrointestinal tract, such as the small intestine or colon. An enteric polymer coating typically resists releases of the active agents until some time after a gastric emptying lag period of about 3-4 hours after administration.

[0117] pH dependent enteric coatings comprises one or more pH-dependent or pH-sensitive polymers that maintain their structural integrity at low pH, as in the stomach, but dissolve in higher pH environments in more distal regions of the gastrointestinal tract, such as the small intestine, where the drug contents are released. For purposes of the present invention, "pH dependent" is defined as having characteristics (*e.g.*, dissolution) which vary according to environmental pH. Exemplary pH-dependent polymers include, but are not limited to, methacarylic acid copolymers, methacrylic acid-methyl methacrylate copolymers (*e.g.,* EUDRAGIT® L100 (Type A), EUDRAGIT® S100 (Type B), Rohm GmbH, Germany; methacrylic acid-ethyl acrylate copolymers (*e.g.*, EUDRAGIT® L100-55 (Type C) and EUDRAGIT® L30D-55 copolymer dispersion, Rohm GmbH, Germany); copolymers of methacrylic acid-methyl methacrylate and methyl methacrylate (EUDRAGIT® FS); terpolymers of methacrylic acid, methacrylate, and ethyl acrylate; cellulose acetate phthalates (CAP); hydroxypropyl methylcellulose phthalate (HPMCP) (*e.g.*, HP-55, HP-50, HP-55S, Shinetsu Chemical, Japan); polyvinyl acetate phthalates (PVAP) (*e.g.*, COATERIC®, OPADRY® enteric white OY-P-7171); cellulose acetate succinates (CAS); hydroxypropyl methylcellulose acetate succinate (HPMCAS), *e.g.*, HPMCAS LF Grade, MF Grade, HF Grade, including AQOAT® LF and AQOAT® MF (Shin-Etsu Chemical, Japan); Shinetsu Chemical, Japan); shellac (*e.g.*, Marcoat™ 125 & Marcoat™ 125N); carboxymethyl ethylcellulose (CMEC, Freund Corporation, Japan), cellulose acetate phthalates (CAP) (*e.g.*, AQUATERIC®); cellulose acetate trimellitates (CAT); and mixtures of two or more thereof at weight ratios between about 2:1 to about 5:1, such as, for instance, a mixture of EUDRAGIT® L 100-55 and EUDRAGIT® S 100 at a weight ratio of about 3:1 to about 2:1, or a mixture of EUDRAGIT® L 30 D-55 and EUDRAGIT® FS at a weight ratio of about 3:1 to about 5:1.

[0118] pH-dependent polymers typically exhibit a characteristic pH optimum for dissolution. In some embodiments, the pH-dependent polymer exhibits a pH optimum between about 5.0 and 5.5, between about 5.5 and 6.0, between about 6.0 and 6.5, or between about 6.5 and 7.0. In other embodiments, the pH-dependent polymer exhibits a pH optimum of ≥5.0, of ≥5.5, of ≥6.0, of ≥6.5, or of ≥7.0.

[0119] In certain embodiment, the coating methodology employs the blending of one or more pH-dependent and one or more pH-independent polymers. The blending of pH-dependent and pH-independent polymers can reduce the release rate of active ingredients once the soluble polymer has reached its optimum pH of solubilization.

[0120] In some embodiments, a "time-controlled" or "time-dependent" release profile can be obtained using a water insoluble capsule body containing one or more active agents, wherein the capsule body closed at one end with an insoluble, but permeable and swellable hydrogel plug. Upon contact with gastrointestinal fluid or dissolution medium, the plug swells, pushing itself out of the capsule and releasing the drugs after a pre-determined lag time, which can be controlled by *e.g.*, the position and dimensions of the plug. The capsule body may be further coated with an outer pH-dependent enteric coating keeping the capsule intact until it reaches the small intestine. Suitable plug materials include, for example, polymethacrylates, erodible compressed polymers (*e.g.*, HPMC, polyvinyl alcohol), congealed melted polymer (*e.g.*, glyceryl mono oleate) and enzymatically controlled erodible polymers (*e.g.*, polysaccharides, such as amylose, arabinogalactan, chitosan, chondroitin sulfate, cyclodextrin, dextran, guar gum, pectin and xylan).

[0121] In other embodiments, capsules or bilayered tablets may be formulated to contain a drug-containing core, covered by a swelling layer, and an outer insoluble, but semi-permeable polymer coating or membrane. The lag time prior to rupture can be controlled by the permeation and mechanical properties of the polymer coating and the swelling behavior of the swelling layer. Typically, the swelling layer comprises one or more swelling agents, such as swellable hydrophilic polymers that swell and retain water in their structures.

[0122] Exemplary water swellable materials to be used in the delayed-release coating include, but are not limited to, polyethylene oxide (having *e.g.*, an average molecular weight between 1,000,000 to 7,000,000, such as POLYOX®), methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose; polyalkylene oxides having a weight average molecular weight of 100,000 to 6,000,000, including but not limited to poly(methylene oxide), poly(butylene oxide); poly(hydroxy alkyl methacrylate) having a molecular weight of from 25,000 to 5,000,000; poly(vinyl)alcohol, having a low acetal residue, which is cross-linked with glyoxal, formaldehyde or glutaraldehyde and having a degree of polymerization of from 200 to 30,000; mixtures of methyl cellulose, cross-linked agar and carboxymethyl cellulose; hydrogel forming copolymers produced by forming a dispersion of a finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, butylene or isobutylene cross-linked with from 0.001 to 0.5 moles of saturated cross-linking agent per mole of maleic anyhydride in the copolymer; CARBOPOL® acidic carboxy polymers having a molecular weight of 450,000 to 4,000,000; CYANAMER® polyacrylamides; cross-linked water swellable indenemaleicanhydride polymers; GOODRITE® polyacrylic acid having a molecular weight of 80,000 to 200,000; starch graft copolymers; AQUA-KEEPS® acrylate

polymer polysaccharides composed of condensed glucose units such as diester cross-linked polyglucan; carbomers having a viscosity of 3,000 to 60,000 mPa as a 0.5%-1% w/v aqueous solution; cellulose ethers such as hydroxypropylcellulose having a viscosity of about 1000-7000 mPa s as a 1% w/w aqueous solution (25° C); hydroxypropyl methylcellulose having a viscosity of about 1000 or higher, preferably 2,500 or higher to a maximum of 25,000 mPa as a 2% w/v aqueous solution; polyvinylpyrrolidone having a viscosity of about 300-700 mPa s as a 10% w/v aqueous solution at 20° C; and combinations thereof.

[0123] Alternatively, the release time of the drugs can be controlled by a disintegration lag time depending on the balance between the tolerability and thickness of a water insoluble polymer membrane (such as ethyl cellulose, EC) containing predefined micropores at the bottom of the body and the amount of a swellable excipient, such as low substituted hydroxypropyl cellulose (L-HPC) and sodium glycolate. After oral administration, GI fluids permeate through the micropores, causing swelling of the swellable excipients, which produces an inner pressure disengaging the capsular components, including a first capsule body containing the swellable materials, a second capsule body containing the drugs, and an outer cap attached to the first capsule body.

[0124] The enteric layer may further comprise anti-tackiness agents, such as talc or glyceryl monostearate and/or plasticizers. The enteric layer may further comprise one or more plasticizers including, but not limited to, triethyl citrate, acetyl triethyl citrate, acetyltributyl citrate, polyethylene glycol acetylated monoglycerides, glycerin, triacetin, propylene glycol, phthalate esters (*e.g.*, diethyl phthalate, dibutyl phthalate), titanium dioxide, ferric oxides, castor oil, sorbitol and dibutyl sebacate.

[0125] In another embodiment, the delayed release formulation employs a water-permeable but insoluble film coating to enclose the active ingredient and an osmotic agent. As water from the gut slowly diffuses through the film into the core, the core swells until the film bursts, thereby releasing the active ingredients. The film coating may be adjusted to permit various rates of water permeation or release time.

[0126] In another embodiment, the delayed release formulation employs a water-impermeable tablet coating whereby water enters through a controlled aperture in the coating until the core bursts. When the tablet bursts, the drug contents are released immediately or over a longer period of time. These and other techniques may be modified to allow for a pre-determined lag period before release of drugs is initiated.

[0127] In another embodiment, the active agents are delivered in a formulation to provide both delayed-release and extended-release (delayed-sustained). The term "delayed-

extended-release" is used herein with reference to a drug formulation providing pulsatile release of active agents at a pre-determined time or lag period following administration, which is then followed by extended-release of the active agents thereafter.

[0128] In some embodiments, immediate-release, extended-release, delayed-release, or delayed-extended-release formulations comprises an active core comprised of one or more inert particles, each in the form of a bead, pellet, pill, granular particle, microcapsule, microsphere, microgranule, nanocapsule, or nanosphere coated on its surfaces with drugs in the form of *e.g.*, a drug-containing film-forming composition using, for example, fluid bed techniques or other methodologies known to those of skill in the art. The inert particle can be of various sizes, so long as it is large enough to remain poorly dissolved. Alternatively, the active core may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer composition containing the drug substance.

[0129] The amount of drug in the core will depend on the dose that is required, and typically varies from about 5 to 90 weight %. Generally, the polymeric coating on the active core will be from about 1 to 50% based on the weight of the coated particle, depending on the lag time and type of release profile required and/or the polymers and coating solvents chosen. Those skilled in the art will be able to select an appropriate amount of drug for coating onto or incorporating into the core to achieve the desired dosage. In one embodiment, the inactive core may be a sugar sphere or a buffer crystal or an encapsulated buffer crystal such as calcium carbonate, sodium bicarbonate, fumaric acid, tartaric acid, etc. which alters the microenvironment of the drug to facilitate its release.

[0130] In some embodiments, for example, delayed-release or delayed-extended-release compositions may formed by coating a water soluble/dispersible drug-containing particle, such as a bead, with a mixture of a water insoluble polymer and an enteric polymer, wherein the water insoluble polymer and the enteric polymer may be present at a weight ratio of from 4:1 to 1:1, and the total weight of the coatings is 10 to 60 weight % based on the total weight of the coated beads. The drug layered beads may optionally include an inner dissolution rate controlling membrane of ethylcellulose. The composition of the outer layer, as well as the individual weights of the inner and outer layers of the polymeric membrane are optimized for achieving desired circadian rhythm release profiles for a given active, which are predicted based on in vitro/in vivo correlations.

[0131] In other embodiments the formulations may comprise a mixture of immediate-release drug-containing particles without a dissolution rate controlling polymer membrane

and delayed-extended-release beads exhibiting, for example, a lag time of 2-4 hours following oral administration, thus providing a two-pulse release profile.

[0132] In some embodiments, the active core is coated with one or more layers of dissolution rate-controlling polymers to obtain desired release profiles with or without a lag time. An inner layer membrane can largely control the rate of drug release following imbibition of water or body fluids into the core, while the outer layer membrane can provide for a desired lag time (the period of no or little drug release following imbibition of water or body fluids into the core). The inner layer membrane may comprise a water insoluble polymer, or a mixture of water insoluble and water soluble polymers.

[0133] The polymers suitable for the outer membrane, which largely controls the lag time of up to 6 hours may comprise an enteric polymer, as described above, and a water insoluble polymer at 10 to 50 weight %. The ratio of water insoluble polymer to enteric polymer may vary from 4:1 to 1:2, preferably the polymers are present at a ratio of about 1:1. The water insoluble polymer typically used is ethylcellulose.

[0134] Exemplary water insoluble polymers include ethylcellulose, polyvinyl acetate (Kollicoat SR#0D from BASF), neutral copolymers based on ethyl acrylate and methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups such as EUDRAGIT® NE, RS and RS30D, RL or RL30D and the like. Exemplary water soluble polymers include low molecular weight HPMC, HPC, methylcellulose, polyethylene glycol (PEG of molecular weight>3000) at a thickness ranging from 1 weight % up to 10 weight % depending on the solubility of the active in water and the solvent or latex suspension based coating formulation used. The water insoluble polymer to water soluble polymer may typically vary from 95:5 to 60:40, preferably from 80:20 to 65:35.

[0135] In some embodiments, AMBERLITE™ IRP69 resin is used as an extended-release carrier. AMBERLITE™ IRP69 is an insoluble, strongly acidic, sodium form cation exchange resin that is suitable as carrier for cationic (basic) substances. In other embodiments, DUOLITE™ AP143/1093 resin is used as an extended-release carrier. DUOLITE™ AP143/1093 is an insoluble, strongly basic, anion exchange resin that is suitable as a carrier for anionic (acidic) substances.

[0136] When used as a drug carrier, AMBERLITE IRP69 or/and DUOLITE™ AP143/1093 resin provides a means for binding medicinal agents onto an insoluble polymeric matrix. Extended-release is achieved through the formation of resin-drug complexes (drug resinates). The drug is released from the resin *in vivo* as the drug reaches equilibrium with the high electrolyte concentrations, which are typical of the gastrointestinal tract. More

hydrophobic drugs will usually elute from the resin at a lower rate, owing to hydrophobic interactions with the aromatic structure of the cation exchange system.

[0137] Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. Therefore, an enteric coated pill will not dissolve in the acidic juices of the stomach (pH ~3), but they will in the alkaline (pH 7-9) environment present in the small intestine. Examples of enteric coating materials include, but are not limited to, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxy propyl methyl cellulose phthalate, hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate), polyvinyl acetate phthalate (PVAP), methyl methacrylate-methacrylic acid copolymers, sodium alginate and stearic acid. In some embodiments, the pharmaceutical composition is formulated for oral administration. Oral dosage forms include, for example, tablets, capsules, caplets, and may also comprise a plurality of granules, beads, powders or pellets that may or may not be encapsulated. Tablets and capsules represent the most convenient oral dosage forms, in which case solid pharmaceutical carriers are employed.

[0138] In a delayed-release formulation, one or more barrier coatings may be applied to pellets, tablets, or capsules to facilitate slow dissolution and concomitant release of drugs into the intestine. Typically, the barrier coating contains one or more polymers encasing, surrounding, or forming a layer, or membrane around the therapeutic composition or active core.

[0139] In some embodiments, the active agents are delivered in a formulation to provide delayed-release at a pre-determined time following administration. The delay may be up to about 10 minutes, about 20 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, or longer.

[0140] Various coating techniques may be applied to granules, beads, powders or pellets, tablets, capsules or combinations thereof containing active agents to produce different and distinct release profiles. In some embodiments, the pharmaceutical composition is in a tablet or capsule form containing a single coating layer. In other embodiments, the pharmaceutical composition is in a tablet or capsule form containing multiple coating layers.

[0141] In some embodiments, the pharmaceutical composition comprises one or more analgesics, one or more α-blockers, and one or more other active ingredients selected from the group consisting of antimuscarinic agents, antidiuretics and spasmolytics. In some embodiments, the pharmaceutical composition comprises one or more analgesics, one or more 5α-reductase inhibitors, and one or more other active ingredients selected from the

group consisting of antimuscarinic agents, antidiuretics, α-blockers and spasmolytics. Examples of antimuscarinic agents include, but are not limited to, oxybutynin, solifenacin, darifenacin and atropine. Examples of antidiuretics include, but are not limited to, antidiuretic hormone (ADH), angiotensin II, aldosterone, vasopressin, vasopressin analogs (*e.g.*, desmopressin argipressin, lypressin, felypressin, ornipressin, terlipressin; vasopressin receptor agonists, atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP) receptor (*i.e.*, NPR1, NPR2, NPR3) antagonists (*e.g.*, HS-142-1, isatin, [Asu7,23']b-ANP-(7-28)], anantin, a cyclic peptide from Streptomyces coerulescens, and 3G12 monoclonal antibody); somatostatin type 2 receptor antagonists (*e.g.*, somatostatin), and pharmaceutically-acceptable derivatives, analogs, salts, hydrates, and solvates thereof. Examples of spasmolytics include, but are not limited to, carisoprodol, benzodiazepines, baclofen, cyclobenzaprine, metaxalone, methocarbamol, clonidine, clonidine analog, and dantrolene.

[0142] In some embodiments, the pharmaceutical composition comprises one or more analgesics and one or more α-blockers. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more α-blockers, and (3) one or more antimuscarinic agents. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more α-blockers and (3) one or more antidiuretics. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more α-blockers, and (3) one or more spasmolytics. In another embodiment, the pharmaceutical composition comprises (1) one or two analgesics, (2) one or more α-blockers, (3) one or two antimuscarinic agents, and (4) one or two antidiuretics. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more α-blockers, (3) one or more spasmolytics agents, and (4) one or more antidiuretics.

[0143] In some embodiments, the pharmaceutical composition comprises one or more analgesics and one or more 5α-reductase inhibitors. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more 5α-reductase inhibitors, and (3) one or more antimuscarinic agents. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more 5α-reductase inhibitors and (3) one or more antidiuretics. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more 5α-reductase inhibitors, and (3) one or more spasmolytics. In another embodiment, the pharmaceutical composition comprises (1) one or two analgesics, (2) one or more 5α-

reductase inhibitors, (3) one or two antimuscarinic agents, and (4) one or two antidiuretics. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more 5α-reductase inhibitors, (3) one or more spasmolytics agents, and (4) one or more antidiuretics.

[0144] In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more 5α-reductase inhibitors, and (3) one or more α-blockers. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more 5α-reductase inhibitors, (3) one or more α-blockers and (4) one or more antidiuretics. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more 5α-reductase inhibitors, (3) one or more α-blockers and (4) one or more spasmolytics. In another embodiment, the pharmaceutical composition comprises (1) one or two analgesics, (2) one or more 5α-reductase inhibitors, (3) one or two antimuscarinic agents, (4) one or two antidiuretics and (5) one or more α-blockers. In another embodiment, the pharmaceutical composition comprises (1) one or more analgesics, (2) one or more 5α-reductase inhibitors, (3) one or more spasmolytics agents, (4) one or more antidiuretics, and (5) one or more α-blockers.

[0145] In one embodiment, the plurality of active ingredients are formulated for immediate-release. In other embodiment, the plurality of active ingredients are formulated for extended-release. In other embodiment, the plurality of active ingredients are formulated for both immediate-release and extended-release (*e.g.*, a first portion of each active ingredient is formulated for immediate-release and a second portion of each active ingredient is formulated for extended-release). In yet other embodiment, some of the plurality of active ingredients are formulated for immediate-release and some of the plurality of active ingredients are formulated for extended-release (*e.g.*, active ingredients A, B, C are formulated for immediate-release and active ingredients C and D are formulated for extended-release). In some other embodiments, the immediate-release component and/or the extended-release component is further coated with a delayed-release coating, such as an enteric coating.

[0146] In certain embodiments, the pharmaceutical composition comprises an immediate-release component and an extended-release component. The immediate-release component may comprise one or more active ingredients selected from the group consisting of analgesics, α-blockers, 5α-reductase inhibitors, antimuscarinic agents, antidiuretics and spasmolytics. The extended-release component may comprise one or more active ingredients selected from the group consisting of analgesics, α-blockers, antimuscarinic agents,

antidiuretics and spasmolytics. In some embodiments, the immediate-release component and the extended-release component have exactly the same active ingredients. In other embodiments, the immediate-release component and the extended-release component have different active ingredients. In yet other embodiments, the immediate-release component and the extended-release component have one or more common active ingredients. In some other embodiments, the immediate-release component and/or the extended-release component is further coated with a delayed-release coating, such as an enteric coating.

[0147] In one embodiment, the pharmaceutical composition comprises two or more active ingredients (*e.g.,* a mixture of one or more analgesic agents, and one or more α-blockers, one or more 5α-reductase inhibitors, one or more antimuscarinic agents or antidiuretics or spasmolytics), formulated for immediate-release at about the same time. In another embodiment, the pharmaceutical composition comprises two or more active ingredients, formulated for extended-release at about the same time. In another embodiment, the pharmaceutical composition comprises two or more active ingredients formulated as two extended-release components, each providing a different extended-release profile. For example, a first extended-release component releases a first active ingredient at a first release rate and a second extended-release component releases a second active ingredient at a second release rate. In another embodiment, the pharmaceutical composition comprises two or more active ingredients, both formulated for delayed release. In another embodiment, the pharmaceutical composition comprises two or more active ingredients formulated for delayed release. In another embodiment, the pharmaceutical composition comprises two or more active ingredients formulated as two delayed-release components, each providing a different delayed-release profile. For example, a first delayed-release component releases a first active ingredient at a first time point and a second delayed-release component releases a second active ingredient at a second time point. In another embodiment, the pharmaceutical composition comprises two or more active ingredients, one or more of which are formulated for immediate-release and the others are formulated for extended-release. In another embodiment, the pharmaceutical composition comprises two or more active ingredients, a fraction of which is formulated for immediate-release and the remainder is formulated for extended-release.

[0148] In some embodiments, the pharmaceutical composition comprises one or more analgesic agents, and one or more α-blockers, 5α-reductase inhibitors, an antidiuretic, wherein the one or more analgesic agents and one or more α-blockers are formulated for delayed release and wherein the antidiuretic is formulated for immediate release. In other

embodiments, the pharmaceutical composition further comprises an additional agent selected from the group consisting of an analgesic agent, α-blocker, a 5α-reductase inhibitor, an antimuscarinic agent, an antidiuretic agent and a spasmolytic, wherein the additional agent is formulated for delayed release. In some embodiments, the delayed release formulation delays the release of the active ingredient for a period of 1, 2, 3, 4 or 5 hours.

[0149] The term "immediate-release" is used herein with reference to a drug formulation that does not contain a dissolution rate controlling material. There is substantially no delay in the release of the active agents following administration of an immediate-release formulation. An immediate-release coating may include suitable materials immediately dissolving following administration so as to release the drug contents therein. Exemplary immediate-release coating materials include gelatin, polyvinyl alcohol polyethylene glycol (PVA-PEG) copolymers (*e.g.*, KOLLICOAT®) and various others materials known to those skilled in the art.

[0150] An immediate-release composition may comprise 100% of the total dosage of a given active agent administered in a single unit dose. Alternatively, an immediate-release component may be included as a component in a combined release profile formulation that may provide about 1% to about 60% of the total dosage of the active agent(s) to be delivered by the pharmaceutical formulation. For example, the immediate-release component may provide about 5%-60%, about 10% to about 60%, about 10% to about 50%, about 10% to about 40%, about 10% to about 30%, about 10% to about 20%, about 20% to about 60%, about 20% to about 50%, about 20% to about 30%, about 30% to about 60%, about 30% to about 50%, about 40% to about 60%, about 40% to about 50%, about 45% to about 60% or about 45% to about 50% of the total dosage of the active agent(s) to be delivered by the formulation. In alternate embodiments, the immediate-release component provides about 2, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55or 60% of the total dosage of the active agent(s) to be delivered by the formulation.

[0151] In some embodiments, the immediate-release or delayed-release formulation comprises an active core comprised of one or more inert particles, each in the form of a bead, pellet, pill, granular particle, microcapsule, microsphere, microgranule, nanocapsule, or nanosphere coated on its surfaces with drugs in the form of *e.g.*, a drug-containing film-forming composition using, for example, fluid bed techniques or other methodologies known to those of skill in the art. The inert particle can be of various sizes, so long as it is large enough to remain poorly dissolved. Alternatively, the active core may be prepared by

granulating and milling and/or by extrusion and spheronization of a polymer composition containing the drug substance.

[0152] The amount of drug in the core will depend on the dose that is required, and typically varies from about 5 to 90 weight %. Generally, the polymeric coating on the active core will be from about 1 to 50% based on the weight of the coated particle, depending on the lag time and type of release profile required and/or the polymers and coating solvents chosen. Those skilled in the art will be able to select an appropriate amount of drug for coating onto or incorporating into the core to achieve the desired dosage. In one embodiment, the inactive core may be a sugar sphere or a buffer crystal or an encapsulated buffer crystal such as calcium carbonate, sodium bicarbonate, fumaric acid, tartaric acid, *etc.* which alters the microenvironment of the drug to facilitate its release.

[0153] In some embodiments, the delayed-release formulation is formed by coating a water soluble/dispersible drug-containing particle, such as a bead, with a mixture of a water insoluble polymer and an enteric polymer, wherein the water insoluble polymer and the enteric polymer may be present at a weight ratio of from 4:1 to 1:1, and the total weight of the coatings is 10 to 60 weight % based on the total weight of the coated beads. The drug layered beads may optionally include an inner dissolution rate controlling membrane of ethylcellulose. The composition of the outer layer, as well as the individual weights of the inner and outer layers of the polymeric membrane are optimized for achieving desired circadian rhythm release profiles for a given active, which are predicted based on *in vitro/in vivo* correlations.

[0154] In other embodiments the formulations comprise a mixture of immediate-release drug-containing particles without a dissolution rate controlling polymer membrane and delayed-release beads exhibiting, for example, a lag time of 2-4 hours following oral administration, thus providing a two-pulse release profile. In yet other embodiments the formulations comprise a mixture of two types of delayed-release beads: a first type that exhibits a lag time of 1-3 hours and a second type that exhibits a lag time of 4-6 hours.

[0155] Preferably, the formulations are designed with release profiles to limit interference with restful sleep, wherein the formulation releases the medicine when the individual would normally be awakened by an urge to urinate. For example, consider an individual who begins sleeping at 11 PM and is normally awakened at 12:30 AM, 3:00 AM, and 6:00 AM to urinate. A delayed, extended-release vehicle could be taken at 10 PM and start delivering the medicine at 12 AM and gradually release the medicine over a period of 5-8 hours, thereby delaying or eliminating the need to urinate. In other embodiments, the

formulations are designed with a release profile that a fraction of the medicine (e.g., 20-60%) is released immediately or within 2 hours of administration and the rest is released over an extended period of time. The pharmaceutical composition may be administered daily or administered on an as needed basis. In certain embodiments, the pharmaceutical composition is administered to the subject prior to bedtime. In some embodiments, the pharmaceutical composition is administered immediately before bedtime. In some embodiments, the pharmaceutical composition is administered within about two hours before bedtime, preferably within about one hour before bedtime. In another embodiment, the pharmaceutical composition is administered about two hours before bedtime. In a further embodiment, the pharmaceutical composition is administered at least two hours before bedtime. In another embodiment, the pharmaceutical composition is administered about one hour before bedtime. In a further embodiment, the pharmaceutical composition is administered at least one hour before bedtime. In a still further embodiment, the pharmaceutical composition is administered less than one hour before bedtime. In still another embodiment, the pharmaceutical composition is administered immediately before bedtime. Preferably, the pharmaceutical composition is administered orally. Suitable compositions for oral administration include, but are not limited to: tablets, coated tablets, dragees, capsules, powders, granulates and soluble tablets, and liquid forms, for example, suspensions, dispersions or solutions.

[0156] The appropriate dosage ("therapeutically effective amount") of the active agent(s) in the immediate-release component or the extended-release component will depend, for example, on the severity and course of the condition, the mode of administration, the bioavailability of the particular agent(s), the age and weight of the patient, the patient's clinical history and response to the active agent(s), discretion of the physician, *etc.*

[0157] As a general proposition, the therapeutically effective amount of the active agent(s) in the immediate-release component, the extended-release component or the delayed-extended-release component is administered in the range of about 100 μg/kg body weight/day to about 100 mg/kg body weight/day whether by one or more administrations. In some embodiments, the range of each active agent administered daily in a single dose or in multiple does is from about 100 μg/kg body weight/day to about 50 mg/kg body weight/day, 100 μg/kg body weight/day to about 10 mg/kg body weight/day, 100 μg/kg body weight/day to about 1 mg/kg body weight/day, 100 μg/kg body weight/day to about 10 mg/kg body weight/day, 500 μg/kg body weight/day to about 100 mg/kg body weight/day, 500 μg/kg body weight/day to about 50 mg/kg body weight/day, 500 μg/kg body weight/ day to about 5

mg/kg body weight/ day, 1 mg/kg body weight/day to about 100 mg/kg body weight/day, 1 mg/kg body weight/day to about 50 mg/kg body weight/ day, 1 mg/kg body weight/day to about 10 mg/kg body weight/day, 5 mg/kg body weight/dose to about 100 mg/kg body weight/day, 5 mg/kg body weight/dose to about 50 mg/kg body weight/day, 10 mg/kg body weight/day to about 100 mg/kg body weight/day, and 10 mg/kg body weight/day to about 50 mg/kg body weight/day.

[0158] The active agent(s) described herein may be included in an immediate-release component or an extended-release component, a delayed-extended-release component or combinations thereof for daily oral administration at a single dose or combined dose range of 1 mg to 2000 mg, 5 mg to 2000 mg, 10 mg to 2000 mg, 50 mg to 2000 mg, 100 mg to 2000 mg, 200 mg to 2000 mg, 500 mg to 2000 mg, 5 mg to 1800 mg, 10 mg to 1600 mg, 50 mg to 1600 mg, 100 mg to 1500 mg, 150 mg to 1200 mg, 200 mg to 1000 mg, 300 mg to 800 mg, 325 mg to 500 mg, 1 mg to 1000 mg, 1 mg to 500 mg, 1 mg to 200 mg, 5 mg to 1000 mg, 5 mg to 500 mg, 5 mg to 200 mg, 10 mg to 1000 mg, 10 mg to 500 mg, 10 mg to 200 mg, 50 mg to 1000 mg, 50 mg to 500 mg, 50 mg to 200 mg, 250 mg to 1000 mg, 250 mg to 500 mg, 500 mg to 1000 mg, 500 mg to 2000 mg. As expected, the dosage will be dependent on the condition, size, age and condition of the patient.

[0159] In some embodiments, the pharmaceutical composition comprises a single analgesic agent, and one or more α-blockers or one or more 5α-reductase inhibitors. In one embodiment, the single analgesic agent is aspirin. In another embodiment, the single analgesic agent is ibuprofen. In another embodiment, the single analgesic agent is naproxen or naproxen sodium. In another embodiment, the single analgesic agent is indomethacin. In another embodiment, the single analgesic agent is nabumetone. In another embodiment, the single analgesic agent is acetaminophen. In another embodiment, the single analgesic agent is acetaminophen and the one or more α-blockers comprise tamsulosin. In another embodiment, the single analgesic agent is acetaminophen and the one or more 5α-reductase inhibitors comprise finasteride.

[0160] In some embodiments, the single analgesic agent is given at a daily dose of 1 mg to 2000 mg, 5 mg to 2000 mg, 20 mg to 2000 mg, 5 mg to 1000 mg, 20 mg to 1000 mg, 50 mg to 500 mg, 100 mg to 500 mg, 250 mg to 500 mg, 250 mg to 1000 mg or 500 mg to 1000 mg. In certain embodiments, the pharmaceutical composition comprises acetylsalicylic acid, ibuprofen, naproxen, naproxen sodium, indomethancin, nabumetone or acetaminophen as a single analgesic agent and the analgesic agent is administered orally at a daily dose in the range of 5 mg to 2000 mg, 20 mg to 2000 mg, 5 mg to 1000 mg, 20 mg to 1000 mg, 50 mg to

500 mg, 100 mg to 500 mg, 250 mg to 500 mg, 250 mg to 1000 mg or 500 mg to 1000 mg. In some embodiments, a second analgesic agent is given at a daily dose of 1 mg to 2000 mg, 5 mg to 2000 mg, 20 mg to 2000 mg, 5 mg to 1000 mg, 20 mg to 1000 mg, 50 mg to 500 mg, 100 mg to 500 mg, 250 mg to 500 mg, 250 mg to 1000 mg or 500 mg to 1000 mg.

[0161] In other embodiments, the pharmaceutical composition comprises a pair of analgesic agents and one or more α-blockers. Examples of such paired analgesic agents include, but are not limited to, acetylsalicylic acid and ibuprofen, acetylsalicylic acid and naproxen sodium, acetylsalicylic acid and nabumetone, acetylsalicylic acid and acetaminophen, acetylsalicylic acid and indomethancin, ibuprofen and naproxen sodium, ibuprofen and nabumetone, ibuprofen and acetaminophen, ibuprofen and indomethancin, naproxen, naproxen sodium and nabumetone, naproxen sodium and acetaminophen, naproxen sodium and indomethancin, nabumetone and acetaminophen, nabumetone and indomethancin, and acetaminophen and indomethancin. The paired analgesic agents are mixed at a weight ratio in the range of 0.1:1 to 10:1, 0.2:1 to 5:1 or 0.3:1 to 3:1, with a combined dose in the range of 5 mg to 2000 mg, 20 mg to 2000 mg, 100 mg to 2000 mg, 200 mg to 2000 mg, 500 mg to 2000 mg, 5 mg to 1500 mg, 20 mg to 1500 mg, 100 mg to 1500 mg, 200 mg to 1500 mg, 500 mg to 1500 mg, 5 mg to 1000 mg, 20 mg to 1000 mg, 100 mg to 1000 mg, 250 mg to 500 mg, 250 mg to 1000 mg, 250 mg to 1500 mg, 500 mg to 1000 mg, 500 mg to 1500 mg, 1000 mg to 1500 mg, and 1000 mg to 2000 mg. In one embodiment, the paired analgesic agents are mixed at a weight ratio of 1:1.

[0162] In some other embodiments, the pharmaceutical composition of the present application further comprises one or more antimuscarinic agents. Examples of the antimuscarinic agents include, but are not limited to, oxybutynin, solifenacin, darifenacin, fesoterodine, tolterodine, trospium and atropine. The daily dose of antimuscarinic agent is in the range of 0.01 mg to 100 mg, 0.1 mg to 100 mg, 1 mg to 100 mg, 10 mg to 100 mg, 0.01 mg to 25 mg, 0.1 mg to 25 mg, 1 mg to 25 mg, 10 mg to 25 mg, 0.01 mg to 10 mg, 0.1 mg to 10 mg, 1 mg to 10 mg, 10 mg to 100 mg and 10 mg to 25 mg.

[0163] In certain embodiments, the pharmaceutical composition comprises one or more α-blockers, an analgesic agent selected from the group consisting of cetylsalicylic acid, ibuprofen, naproxen, naproxen sodium, nabumetone, acetaminophen and indomethancin, and an antimuscarinic agent selected from the group consisting of oxybutynin, solifenacin, darifenacin and atropine.

[0164] Another aspect of the present application relates to a method for reducing the frequency of urination by administering to a person in need thereof a pharmaceutical

composition formulated in an immediate-release formulation. The pharmaceutical composition comprises one or more analgesic agents and one or more additional active ingredients selected from the group consisting of 5α-reductase inhibitors, α-blockers, antimuscarinic agents, antidiuretic agents and spasmolytics. The pharmaceutical composition may be formulated into a tablet, capsule, dragee, powder, granulate, liquid, gel or emulsion form. Said liquid, gel or emulsion may be ingested by the subject in naked form or contained within a capsule.

[0165] In certain embodiments, the analgesic agent is selected from the group consisting of salicylates, aspirin, salicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, para-aminophenol derivatives, acetanilide, acetaminophen, phenacetin, fenamates, mefenamic acid, meclofenamate, sodium meclofenamate, heteroaryl acetic acid derivatives, tolmetin, ketorolac, diclofenac, propionic acid derivatives, ibuprofen, naproxen sodium, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin; enolic acids, oxicam derivatives, piroxicam, meloxicam, tenoxicam, ampiroxicam, droxicam, pivoxicam, pyrazolon derivatives, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone, coxibs, celecoxib, rofecoxib, nabumetone, apazone, nimesulide, indomethacin, sulindac, etodolac, diflunisal and isobutylphenyl propionic acid. The antimuscarinic agent is selected from the group consisting of oxybutynin, solifenacin, darifenacin and atropine.

[0166] In some embodiments, the pharmaceutical composition comprises a single analgesic agent, a single α-blocker and a single antimuscarinic agent. In some embodiments, the pharmaceutical composition comprises a single analgesic agent, a single 5α-reductase inhibitor and a single antimuscarinic agent. In one embodiment, the single analgesic agent is aspirin. In another embodiment, the single analgesic agent is ibuprofen. In another embodiment, the single analgesic agent is naproxen or naproxen sodium. In another embodiment, the single analgesic agent is indomethacin. In another embodiment, the single analgesic agent is nabumetone. In another embodiment, the single analgesic agent is acetaminophen. In another embodiment, the single α-blocker is tamsulosin. The analgesic agent, α-blocker, 5α-reductase inhibitor and antimuscarinic agent may be given at doses in the ranges described above. In some embodiments, the pharmaceutical composition further comprises an antidiuretic agent or a spasmolytic.

[0167] In some embodiments, the pharmaceutical composition comprises one or more analgesic agents, individually or in combination, in an amount between 50-2000 mg, 50-1500 mg, 50-1200 mg, 50-1000 mg, 50-800 mg, 50-600 mg, 50-500 mg, 50-400 mg, 50-300 mg, 50-250 mg, 50-200 mg, 50-150 mg, 50-100 mg, 100-2000 mg, 100-1500 mg, 100-1200 mg,

100-1000 mg, 100-800 mg, 100-600 mg, 100-400 mg, 100-250 mg, 250-2000 mg, 250-1500 mg, 250-1200 mg, 250-1000 mg, 250-800 mg, 250-600 mg, 250-400 mg, 400-2000 mg, 400-1500 mg, 400-1200 mg, 400-1000 mg, 400-800 mg, 400-600 mg, 600-2000 mg, 600-1500 mg, 600-1200 mg, 600-1000 mg, 600-800 mg, 800-2000 mg, 800-1500 mg, 800-1200 mg, 800-1000 mg, 1000-2000 mg, 1000-1500 mg, 1000-1200 mg, 1200-2000 mg, 1200-1500 mg or 1500-2000 mg, wherein the composition is formulated for extended release with a release profile in which the one or more analgesic agents are released continuously over a period of 5-24 hours, 5-8, 8-16 hours or 16-24 hours.

[0168] In some embodiments, the composition is formulated for extended release with a release profile in which at least 90% of the active ingredients are released continuously over a period of 5-24 hours, 5-8, 8-16 hours or 16-24 hours.

[0169] In some embodiments, the composition is formulated for extended release with a release profile in which the active ingredients are released continuously over a period of 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours.

[0170] In other embodiments, the composition is formulated for extended release with a release profile in which the active ingredients and are released at a steady rate over a period of 5-24 hours, 5-8, 8-16 hours or 16-24 hours. In other embodiments, the composition is formulated for extended release with a release profile in which the active ingredients are released at a steady rate over a period of 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours. As used herein, "a steady rate over a period of time" is defined as a release profile in which the release rate at any point during a given period of time is within 30% - 300% of the average release rate over that given period of time. For example, if 80 mg of aspirin is released at a steady rate over a period of 8 hours, the average release rate is 10 mg/hr during this period of time and the actual release rate at any time during this period is within the range of 3 mg/hr to 30 mg/hr (*i.e.*, within 30% - 300% of the average release rate of 10 mg/hr during the 8 hour period).

[0171] In some embodiments, the analgesic agent is selected from the group consisting of aspirin, ibuprofen, naproxen sodium, naproxen, indomethacin, nabumetone and acetaminophen. The pharmaceutical composition is formulated to provide a steady release of small amount of the analgesic agent to maintain an effective drug concentration in the blood such that the overall amount of the drug in a single dosage is reduced compared to the immediate release formulation. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0172] In some embodiments, the pharmaceutical composition comprises 50-400 mg, 50-250 mg, 250-400 mg or 400-600 mg of an analgesic agent formulated for extended release with a release profile in which at least 90% of the analgesic agent is released continuously, or at a steady rate, over a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0173] In one particular embodiment, the pharmaceutical composition comprises 50-250 mg of acetaminophen formulated for extended release with a release profile in which at least 90% of acetaminophen is released continuously, or at a steady rate, over a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0174] In another particular embodiment, the pharmaceutical composition comprises 250-400 mg of acetaminophen formulated for extended release with a release profile in which 90% of acetaminophen is released continuously, or at a steady rate over a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0175] In another particular embodiment, the pharmaceutical composition comprises 400-600 mg of acetaminophen formulated for extended release with a release profile in which 90% of acetaminophen is released continuously, or at a steady rate over a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0176] In another particular embodiment, the pharmaceutical composition comprises 600-800 mg of acetaminophen formulated for extended release with a release profile in which 90% of acetaminophen is released continuously, or at a steady rate over a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0177] In yet another embodiment, the pharmaceutical composition comprises 800-1000 mg of acetaminophen formulated for extended release with a release profile in which at least 90% of acetaminophen is released continuously, or at a steady rate over a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0178] In some other embodiments, the pharmaceutical composition comprises one or more analgesic agent(s), individually or in combination, in an amount between 50-2000 mg, 50-1500 mg, 50-1200 mg, 50-1000 mg, 50-800 mg, 50-600 mg, 50-500 mg, 50-400 mg, 50-300 mg, 50-250 mg, 50-200 mg, 100-2000 mg, 100-1500 mg, 100-1200 mg, 100-1000 mg,

100-800 mg, 100-600 mg, 100-500 mg, 100-400 mg, 100-300 mg, 100-200 mg, 200-2000 mg, 200-1500 mg, 200-1200 mg, 200-1000 mg, 200-800 mg, 200-600 mg, 200-400 mg, 400-2000 mg, 400-1500 mg, 400-1200 mg, 400-1000 mg, 400-800 mg, 400-600 mg, 600-2000 mg, 600-1500 mg, 600-1200 mg, 600-1000 mg, 600-800 mg, 800-2000 mg, 800-1500 mg, 800-1200 mg, 800-1000 mg, 1000-2000 mg, 1000-1500 mg, 1000-1200 mg, 1200-2000 mg, 1200-1500 mg or 1500-2000 mg, wherein the analgesic agent(s) are formulated for extended release, characterized by a two-phase release profile in which 20-50% of the analgesic agent(s) are released within 2 hours of administration and the remainder are released continuously, or at a steady rate, over a period of 5-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0179] In yet another embodiment, the analgesic agent(s) is formulated for extended release with a two-phase release profile in which 20, 30, 40 or 50% of the analgesic agent(s) are released within 2 hours of administration and the remainder are released continuously, or at a steady rate, over a period of 5-8, 8-16 or 16-24 hours. In one embodiment, the analgesic agent(s) are selected from the group consisting of aspirin, ibuprofen, naproxen sodium, naproxen, indomethacin, nabumetone and acetaminophen. In another embodiment, the analgesic agent is acetaminophen. In some embodiments, the pharmaceutical composition further comprises an antimuscarinic agent, an antidiuretic agent or a spasmolytic. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0180] In another embodiment, the pharmaceutical composition comprises 50-400 mg of acetaminophen formulated for extended release with a two-phase release profile in which 20%, 30%, 40% or 50% of the acetaminophen is released within 2 hours of administration and the remainder is released continuously, or at a steady rate, over a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0181] In another embodiment, the pharmaceutical composition comprises 100-300 mg of acetaminophen formulated for extended release with a two-phase release profile in which 20%, 30%, 40% or 50% of the acetaminophen is released within 2 hours of administration and the remainder is released at a steady rate over a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0182] In another embodiment, the pharmaceutical composition comprises 400-600 mg of acetaminophen formulated for extended release with a two-phase release profile in

which 20%, 30%, 40% or 50% of the acetaminophen is released within 2 hours of administration and the remainder is released continuously, or at a steady rate, in a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0183] In another embodiment, the pharmaceutical composition comprises 600-800 mg of acetaminophen formulated for extended release with a two-phase release profile in which 20%, 30%, 40% or 50% of the acetaminophen is released within 2 hours of administration and the remainder is released continuously, or at a steady rate, in a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0184] In another embodiment, the pharmaceutical composition comprises 800-1000 mg of acetaminophen formulated for extended release with a two-phase release profile in which 20%, 30%, 40% or 50% of the acetaminophen is released within 2 hours of administration and the remainder is released continuously, or at a steady rate, in a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0185] In another embodiment, the pharmaceutical composition comprises 1000-1200 mg of acetaminophen formulated for extended release with a two-phase release profile in which 20%, 30%, 40% or 50% of the acetaminophen is released within 2 hours of administration and the remainder is released continuously, or at a steady rate, in a period of 5-8, 8-16 or 16-24 hours. The other active ingredients may be released immediately after administration or released with the analgesic agent.

[0186] Another aspect of the present application relates to a method for treating nocturia by administering to a subject in need thereof (1) one or more analgesic agents, (2) an α-blocker or a 5α-reductase inhibitor or both, and (3) one or more antidiuretic agents. In certain embodiments, the antidiuretic agent(s) act to: (1) increase vasopressin secretion; (2) increase vasopressin receptor activation; (3) reduce secretion of atrial natriuretic peptide (ANP) or C-type natriuretic peptide (CNP); or (4) reduce ANP and/or CNP receptor activation.

[0187] Exemplary antidiuretic agents include, but are not limited to, antidiuretic hormone (ADH), angiotensin II, aldosterone, vasopressin, vasopressin analogs (*e.g.*, desmopressin argipressin, lypressin, felypressin, ornipressin, terlipressin); vasopressin receptor agonists, atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP) receptor (*i.e.*, NPR1, NPR2, NPR3) antagonists (*e.g.*, HS-142-1, isatin, [Asu7,23']b-ANP-(7-

28)], anantin, a cyclic peptide from Streptomyces coerulescens, and 3G12 monoclonal antibody); somatostatin type 2 receptor antagonists (*e.g.*, somatostatin), and pharmaceutically-acceptable derivatives, analogs, salts, hydrates, and solvates thereof.

[0188] In certain embodiments, the one or more analgesic agents, the α-blocker and/or the 5α-reductase inhibitor are formulated for extended release, and the one or more antidiuretic agents are formulated for immediate release. In other embodiments, the one or more analgesic agents, the α-blocker and/or the 5α-reductase inhibitor are formulated for delayed release and the antidiuretic is formulated for immediate release. In some embodiments, the delayed release formulation delays the release of the active ingredient (e.g., the analgesic agent, antimuscarinic agent, antidiuretic agent and spasmolytic) for a period of 1, 2, 3, 4 or 5 hours.

[0189] Another aspect of the present application relates to a method for reducing the frequency of urination by administering to a person in need thereof a first pharmaceutical composition comprising a diuretic, followed with a second pharmaceutical composition comprising (1) one or more analgesic agents and (1) one or more α-blockers, one or more 5α-reductase inhibitors, or both. The first pharmaceutical composition is dosed and formulated to have a diuretic effect within 6 hours of administration and is administered at least 8 or 7 hours prior to bedtime. The second pharmaceutical composition is administered within 2 hours prior to bedtime. The first pharmaceutical composition is formulated for immediate-release and the second pharmaceutical composition is formulated for extended-release or delayed, extended-release.

[0190] Examples of diuretics include, but are not limited to, acidifying salts, such as $CaCl_2$ and NH_4Cl; arginine vasopressin receptor 2 antagonists, such as amphotericin B and lithium citrate; aquaretics, such as Goldenrod and Junipe; Na-H exchanger antagonists, such as dopamine; carbonic anhydrase inhibitors, such as acetazolamide and dorzolamide; loop diuretics, such as bumetanide, ethacrynic acid, furosemide and torsemide; osmotic diuretics, such as glucose and mannitol; potassium-sparing diuretics, such as amiloride, spironolactone, triamterene, potassium canrenoate; thiazides, such as bendroflumethiazide and hydrochlorothiazide; and xanthines, such as caffeine, theophylline and theobromine.

[0191] In some embodiments, the second pharmaceutical composition further comprises one or more antimuscarinic agents. Examples of the antimuscarinic agents include, but are not limited to, oxybutynin, solifenacin, darifenacin, fesoterodine, tolterodine, trospium and atropine. The second pharmaceutical composition may be formulated in immediate-release formulation or delayed-release formulation or extended-release

formulation. In some other embodiments, the second pharmaceutical composition further comprises one or more antidiuretic agents. In some other embodiments, the second pharmaceutical composition further comprises one or more spasmolytics. Another aspect of the present application relates to a method for reducing the frequency of urination by administering to a subject in need thereof, two or more analgesic agents alternatively to prevent the development of drug resistance. In one embodiment, the method comprises administering a first analgesic agent for a first period of time and then administering a second analgesic agent for a second period of time. In another embodiment, the method further comprises administering a third analgesic agent for a third period of time. The first, second and third analgesic agents are different from each other and at least one of which is formulated for extended-release or delayed, extended-release. In one embodiment, the first analgesic agent is acetaminophen, the second analgesic agent is ibuprofen and the third analgesic agent is naproxen sodium. The length of each period may vary depending on the subject's response to each analgesic agent. In some embodiments, each period lasts from 3 days to three weeks. In another embodiment, the first, second and third analgesic are all formulated for extended-release or delayed, extended-release.

[0192] Another aspect of the present application relates to a pharmaceutical composition comprising a plurality of active ingredients and a pharmaceutically acceptable carrier, wherein at least one of the plurality of active ingredients is formulated for extended-release or delayed, extended-release. In some embodiments, the plurality of active ingredients comprises one or more analgesics and one or more antidiuretic agents. In other embodiments, the plurality of active ingredients comprises one or more analgesics, one or more α-blockers, one or more 5α-reductase inhibitors and one or more antimuscarinic agents. In other embodiments, the plurality of active ingredients comprises one or more analgesics, one or more α-blockers, one or more antidiuretic agents and one or more antimuscarinic agent. In other embodiments, the pharmaceutical composition comprises two different analgesics selected from the group consisting of cetylsalicylic acid, ibuprofen, naproxen sodium, naproxen, nabumetone, acetaminophen and indomethancin. In yet other embodiments, the pharmaceutical composition comprises one analgesic selected from the group consisting of cetylsalicylic acid, ibuprofen, naproxen sodium, nabumetone, acetaminophen and indomethancin; one or more α-blockers and an antimuscarinic agent selected from the group consisting of oxybutynin, solifenacin, darifenacin and atropine.

[0193] In other embodiments, the pharmaceutical composition of the present application further comprises one or more spasmolytics and/or one or more antidiuretics.

Examples of spasmolytics include, but are not limited to, carisoprodol, benzodiazepines, baclofen, cyclobenzaprine, metaxalone, methocarbamol, clonidine, clonidine analog, and dantrolene. In some embodiments, the spasmolytics is used at a daily dose of 1 mg to 1000 mg, 1 mg to 100 mg, 10 mg to 1000 mg, 10 mg to 100 mg, 20 mg to 1000 mg, 20 mg to 800 mg, 20 mg to 500 mg, 20 mg to 200 mg, 50 mg to 1000 mg, 50 mg to 800 mg, 50 mg to 200 mg, 100 mg to 800 mg, 100 mg to 500 mg, 200 mg to 800 mg, and 200 mg to 500 mg. The spasmolytics may be formulated, alone or together with other active ingredient(s) in the pharmaceutical composition, for immediate-release, extended-release, delayed-extended-release or combinations thereof.

[0194] In some embodiments, the pharmaceutical composition comprises one or more analgesic agents selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone and acetaminophen in a total amount of 50-400 mg per agent, one or more α-blockers and one or more antimuscarinic agents selected from the group consisting of oxybutynin, solifenacin, darifenacin and atropine in a total amount of 1-25 mg, wherein the pharmaceutical composition is formulated for extended release with a two-phase release profile in which 20-60% of the active ingredients are released within 2 hours of administration, and the remainder of the active ingredients are released continuously, or at a steady rate, in a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0195] In some embodiments, the pharmaceutical composition comprises one or more analgesic agents selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone and acetaminophen in an amount of 50-400 mg per agent, one or more α-blockers and one or more antidiuretic agents selected from the group consisting of antidiuretic hormone (ADH), angiotensin II, aldosterone, vasopressin, vasopressin analogs (*e.g.*, desmopressin argipressin, lypressin, felypressin, ornipressin, terlipressin); vasopressin receptor agonists, atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP) receptor (*i.e.*, NPR1, NPR2, NPR3) antagonists (*e.g.*, HS-142-1, isatin, [Asu7,23']b-ANP-(7-28)], anantin, a cyclic peptide from Streptomyces coerulescens, and 3G12 monoclonal antibody); somatostatin type 2 receptor antagonists (*e.g.*, somatostatin), and pharmaceutically-acceptable derivatives, analogs, salts, hydrates, and solvates thereof, wherein the pharmaceutical composition is formulated for extended release with a two-phase release profile in which 20-60% of the active ingredients are released within 2 hours of administration, and the remainder are released continuously, or at a steady rate, in a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0196] In some embodiments, the pharmaceutical composition comprises (1)one or more analgesic agents selected from the group consisting of aspirin, ibuprofen, naproxen , naproxen sodium, indomethacin, nabumetone and acetaminophen in an amount of 50-400 mg per agent, (2) one or more α-blockers, or one or more 5α-reductase inhibitors, or both, and (3) one or more spasmolytics selected from the group consisting of carisoprodol, benzodiazepines, baclofen, cyclobenzaprine, metaxalone, methocarbamol, clonidine, clonidine analog, and dantrolene in a total amount of 50-500 mg, wherein the pharmaceutical composition is formulated for extended release with a two-phase release profile in which 20-60% of the active ingredients are released within 2 hours of administration, and the remainder are released continuously, or at a steady rate, in a period of 5-24 hours, 5-8 hours, 8-16 hours or 16-24 hours.

[0197] As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, sweeteners and the like. The pharmaceutically acceptable carriers may be prepared from a wide range of materials including, but not limited to, flavoring agents, sweetening agents and miscellaneous materials such as buffers and absorbents that may be needed in order to prepare a particular therapeutic composition. The use of such media and agents with pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated.

[0198] The present invention is further illustrated by the following example which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are incorporated herein by reference.

EXAMPLE 1: INHIBITION OF THE URGE TO URINATE

[0199] Twenty volunteer subjects, both male and female were enrolled, each of which experienced premature urge or desire to urinate, interfering with their ability to sleep for a sufficient period of time to feel adequately rested. Each subject ingested 400-800 mg of ibuprofen as a single dose prior to bedtime. At least 14 subjects reported that they were able to rest better because they were not being awakened as frequently by the urge to urinate.

[0200] Several subjects reported that after several weeks of nightly use of ibuprofen, the benefit of less frequent urges to urinate was no longer being realized. However, all of these subjects further reported the return of the benefit after several days of abstaining from taking the dosages.

EXAMPLE 2: EFFECT OF ANALGESIC AGENTS, BOTULINUM NEUROTOXIN AND

ANTIMUSCARINIC AGENTS ON MACROPHAGE RESPONSES TO INFLAMMATORY AND NON-INFLAMMATORY STIMULI

Experimental Design

[0201] This study is designed to determine the dose and *in vitro* efficacy of analgesics and antimuscarinic agents in controlling macrophage response to inflammatory and non-inflammatory stimuli mediated by COX2 and prostaglandins (PGE, PGH, *etc.*). It establishes baseline (dose and kinetic) responses to inflammatory and non-inflammatory effectors in bladder cells. Briefly, cultured cells are exposed to analgesic agents and/or antimuscarinic agents in the absence or presence of various effectors.

[0202] The effectors include: lipopolysaccharide (LPS), an inflammatory agent and Cox2 inducer, as inflammatory stimuli; carbachol or acetylcholine, a stimulator of smooth muscle contraction, as non-inflammatory stimuli; botulinum neurotoxin A, a known inhibitor of acetylcholine release, as positive control; and arachidonic acid (AA), gamma linolenic acid (DGLA) or eicosapentaenoic acid (EPA) as precursors of prostaglandins, which are produced following the sequential oxidation of AA, DGLA or EPA inside the cell by cyclooxygenases (COX1 and COX2) and terminal prostaglandin synthases.

[0203] The analgesic agents include: Salicylates such as aspirin, iso-butyl-propanoic-phenolic acid derivative (ibuprofen) such as Advil, Motrin, Nuprin, and Medipren, naproxen sodium such as Aleve, Anaprox, Antalgin, Feminax Ultra, Flanax, Inza, Midol Extended Relief, Nalgesin, Naposin, Naprelan, Naprogesic, Naprosyn, Naprosyn suspension, EC-Naprosyn, Narocin, Proxen, Synflex and Xenobid, acetic acid derivative such as indomethacin (Indocin),1-naphthaleneacetic acid derivative such as nabumetone or relafen, N-acetyl-para-aminophenol (APAP) derivative such as acetaminophen or paracetamol (Tylenol) and Celecoxib.

[0204] The antimuscarinic agents include: oxybutynin, solifenacin, darifenacin and atropine.

[0205] Macrophages are subjected to short term (1-2 hrs) or long term (24-48 hrs) stimulation with:

1) Each analgesic agent alone at various doses.

(2) Each analgesic agent at various doses in the presence of LPS.

(3) Each analgesic agent at various doses in the presence of carbachol or acetylcholine.

(4) Each analgesic agent at various doses in the presence of AA, DGLA, or EPA.

(5) Botulinum neurotoxin A alone at various doses.

(6) Botulinum neurotoxin A at various doses in the presence of LPS.

(7) Botulinum neurotoxin A at various doses in the presence of carbachol or acetylcholine.

(8) Botulinum neurotoxin A at various doses in the presence of AA, DGLA, or EPA.

(9) Each antimuscarinic agent alone at various doses.

(10) Each antimuscarinic agent at various doses in the presence of LPS.

(11) Each antimuscarinic agent at various doses in the presence of carbachol or acetylcholine.

(12) Each antimuscarinic agent at various doses in the presence of AA, DGLA, or EPA.

[0206] The cells are then analyzed for the release of PGH_2, PGE, PGE_2, Prostacydin, Thromboxane, IL-1β, IL-6, TNF-α, the COX2 activity, the production of cAMP and cGMP, the production of IL-1β, IL-6, TNF-α and COX2 mRNA, and surface expression of CD80, CD86 and MHC class II molecules.

Materials and Methods

Macrophage cells

[0207] Murine RAW264.7 or J774 macrophage cells (obtained from ATCC) were used in this study. Cells were maintained in a culture medium containing RPMI 1640 supplemented with 10 % fetal bovine serum (FBS), 15 mM HEPES, 2 mM L-glutamine, 100 U/ml penicillin, and 100 μg / ml of streptomycin. Cells were cultured at 37° C in a 5 % CO_2 atmosphere and split (passages) once a week.

***In vitro* treatment of macrophage cells with analgesics**

[0208] RAW264.7 macrophage cells were seeded in 96-well plates at a cell density of $1.5x10^5$ cells per well in 100 μl of the culture medium. The cells were treated with (1) various concentrations of analgesic (acetaminophen, aspirin, ibuprophen or naproxen), (2) various concentrations of lipopolysaccharide (LPS), which is an effector of inflammatory stimuli to macrophage cells, (3) various concentrations of carbachol or acetylcholine, which are effectors of non-inflammatory stimuli, (4) analgesic and LPS or (5) analgesic and carbachol or acetylcholine. Briefly, the analgesics were dissolved in FBS-free culture medium (*i.e.*, RPMI 1640 supplemented with 15 mM HEPES, 2 mM L-glutamine, 100 U / ml penicillin, and 100 μg / ml of streptomycin), and diluted to desired concentrations by serial dilution with the same medium. For cells treated with analgesic in the absence of LPS, 50 μl of analgesic solution and 50 μl of FBS-free culture medium were added to each well. For cells treated with analgesic in the presence of LPS, 50 μl of analgesic solution and 50 μl of LPS (from *Salmonella typhimurium*) in FBS-free culture medium were added to each well. All conditions were tested in duplicates.

[0209] After 24 or 48 hours of culture, 150 µl of culture supernatants were collected, spun down for 2 min at 8,000 rpm at 4°C to remove cells and debris and stored at -70°C for analysis of cytokine responses by ELISA. The cells were collected and washed by centrifugation (5 min at 1,500 rpm at 4°C) in 500 µl of Phosphate buffer (PBS). Half of the cells were then snap frozen in liquid nitrogen and stored at -70°C. The remaining cells were stained with fluorescent monoclonal antibodies and analyzed by flow cytometry.

Flow cytometry analysis of co-stimulatory molecule expression

[0210] For flow cytometry analysis, macrophages were diluted in 100 µl of FACS buffer (phosphate buffered saline (PBS) with 2% bovine serum albumin (BSA) and 0.01% NaN_3) and stained 30 min at 4°C by addition of FITC-conjugated anti-CD40, PE-conjugated anti-CD80, PE-conjugated anti-CD86 antibody, anti MHC class II ($I\text{-}A^d$) PE (BD Bioscience). Cells were then washed by centrifugation (5 min at 1,500 rpm at 4°C) in 300 µl of FACS buffer. After a second wash, cells were re-suspended in 200 µl of FACS buffer and the percentage of cells expressing a given marker (single positive), or a combination of markers (double positive) were analyzed with the aid of an Accuri C6 flow cytometer (BD Biosciences).

Analysis of cytokine responses by ELISA

[0211] Culture supernatants were subjected to cytokine-specific ELISA to determine IL-1β, IL-6 and TNF-α responses in cultures of macrophages treated with analgesic, LPS alone or a combination of LPS and analgesic. The assays were performed on Nunc MaxiSorp Immunoplates (Nunc) coated overnight with 100 µl of anti-mouse IL-6, TNF-α mAbs (BD Biosciences) or IL-1β mAb (R&D Systems) in 0.1 M sodium bicarbonate buffer (pH 9.5). After two washes with PBS (200 µl per well), 200 µl of PBS 3% BSA were added in each well (blocking) and the plates incubated for 2 hours at room temperature. Plates were washed again two times by addition of 200 µl per well, 100 µl of cytokine standards and serial dilutions of culture supernatants were added in duplicate and the plates were incubated overnight at 4°C. Finally, the plates were washed twice and incubated with 100 µl of secondary biotinylated anti-mouse IL-6, TNFα mAbs (BD Biosciences) or IL-1β (R&D Systems) followed by peroxidase-labelled goat anti-biotin mAb (Vector Laboratories). The colorimetric reaction was developed by the addition of 2,2'-azino-bis (3)-ethylbenzylthiazoline-6-sulfonic acid (ABTS) substrate and H_2O_2 (Sigma) and the absorbance measured at 415 nm with a Victor® V multilabel plate reader (PerkinElmer).

Determination of COX2 activity and the production of cAMP and cGMP

[0212] The COX2 activity in the cultured macrophages is determined by sequential competitive ELISA (R&D Systems). The production of cAMP and cGMP is determined by the cAMP assay and cGMP assay. These assays are performed routinely in the art.

Results

[0213] Table 1 summarizes the experiments performed with Raw 264 macrophage cell line and main findings in terms of the effects of analgesics on cell surface expression of costimulatory molecules CD40 and CD80. Expression of these molecules is stimulated by COX2 and inflammatory signals and thus, was evaluated to determine functional consequences of inhibition of COX2.

[0214] As shown in Table 2, acetaminophen, aspirin, ibuprophen and naproxen inhibit basal expression of co-stimulatory molecules CD40 and CD80 by macrophages at all the tested doses (*i.e.*, 5x 10^5 nM, 5x 10^4 nM, 5x 10^3 nM, 5x 10^2 nM, 50 nM and 5 nM), except for the highest dose (*i.e.,* 5x 10^6 nM), which appears to enhance, rather than inhibit, expression of the co-stimulatory molecules. As shown in Figures 1A and 1B, such inhibitory effect on CD40 and CD50 expression was observed at analgesic doses as low as 0.05 nM (*i.e.*, 0.00005 μM). This finding supports the notion that a controlled release of small doses of analgesic may be preferable to acute delivery of large doses. The experiment also revealed that acetaminophen, aspirin, ibuprophen and naproxen have a similar inhibitory effect on LPS induced expression of CD40 and CD80.

Table 1. Summary of experiments

	Control	LPS *Salmonella typhimurium*	Acetaminophen	Aspirin	Ibuprophen	Naproxen
TESTS						
1	X					
2	X	Dose responses (0, 5, 50, 1000) ng/mL				
3	X		Dose responses (0, 5, 50, 500, 5x10^3, 5x10^4, 5x10^5, 5x10^6) nM			
4	X	X (5 ng/mL) X (50 ng/mL X (1000 ng/mL)	Dose responses (0, 5 , 50, 500, 5x10^3, 5x10^4, 5x10^5, 5x10^6) nM			
ANALYSIS						
a	Characterization of activation/stimulatory status: Flow cytometry analysis of CD40, CD80, CD86 and MHC class II					
b	Mediators of inflammatory responses: ELISA analysis of IL-1β, IL-6, TNF-α					

Table 2. Summary of main findings

Effectors	% Positive	Negative Control	LPS 5 ng/ml	Dose analgesic (nM)						
				$5x10^6$	$5x10^5$	$5x10^4$	$5x10^3$	500	50	5
	$CD40^+CD80^+$	20.6	77.8							
Acetaminophen	$CD40^+CD80^+$			63	18	12	9.8	8.3	9.5	7.5
Aspirin	$CD40^+CD80^+$			44	11	10.3	8.3	8	10.5	7.5
Ibuprophen	$CD40^+CD80^+$			ND*	6.4	7.7	7.9	6.0	4.9	5.8
Naproxen	$CD40^+CD80^+$			37	9.6	7.7	6.9	7.2	6.8	5.2
				Analgesic plus LPS						
Acetaminophen	$CD40^+CD80^+$			95.1	82.7	72.4	68.8	66.8	66.2	62.1
Aspirin	$CD40^+CD80^+$			84.5	80	78.7	74.7	75.8	70.1	65.7
Ibuprophen	$CD40^+CD80^+$			ND	67	77.9	72.9	71.1	63.7	60.3
Naproxen	$CD40^+CD80^+$			66.0	74.1	77.1	71.0	68.8	72	73

* ND: not done (toxicity)

[0215] Table 3 summarizes the results of several studies that measured serum levels of analgesic after oral therapeutic doses in adult humans. As shown in Table 3, the maximum serum levels of analgesic after an oral therapeutic dose are in the range of 10^4 to 10^5 nM. Therefore, the doses of analgesic tested *in vitro* in Table 2 cover the range of concentrations achievable *in vivo* in humans.

Table 3. Serum levels of analgesic in human blood after oral therapeutic doses

Analgesic drug	Molecular weight	Maximum serum levels after oral therapeutic doses		References
		mg/L	nM	
Acetaminophen (Tylenol)	151.16	11-18	$7.2x10^4$-$1.19x10^5$	* BMC Clinical Pharmacology.2010, 10:10 * Anaesth Intensive Care. 2011, 39:242
Aspirin (Acetylsalicylic acid)	181.66	30-100	$1.65x10^5$-$5.5x10^5$	* *Disposition of Toxic Drugs and Chemicals in Man*, 8th Edition, Biomedical Public, Foster City, CA, 2008, pp. 22-25 * J Lab Clin Med. 1984 Jun;103:869
Ibuprofen (Advil, Motrin)	206.29	24-32	$1.16x10^5$-$1.55\ x10^5$	* BMC Clinical Pharmacology2010, 10:10 * J Clin Pharmacol. 2001, 41:330
Naproxen (Aleve)	230.26	Up to 60	Up to $2.6x10^5$	* J Clin Pharmacol. 2001, 41:330

EXAMPLE 3: EFFECT OF ANALGESIC AGENTS, BOTULINUM NEUROTOXIN AND ANTIMUSCARINIC AGENTS ON MOUSE BLADDER SMOOTH MUSCLE CELL RESPONSES TO INFLAMMATORY AND NON-INFLAMMATORY STIMULI

Experimental Design

[0216] This study is designed to characterize how the optimal doses of analgesics determined in Example 2 affect bladder smooth muscle cells in cell culture or tissue cultures, and to address whether different classes of analgesics can synergize to more efficiently inhibit COX2 and PGE2 responses.

[0217] The effectors, analgesic agents and antimuscarinic agents are described in Example 2.

[0218] Primary culture of mouse bladder smooth muscle cells are subjected to short term (1-2 hrs) or long term (24-48 hrs) stimulation with:

(1) Each analgesic agent alone at various doses.

(2) Each analgesic agent at various doses in the presence of LPS.

(3) Each analgesic agent at various doses in the presence of carbachol or acetylcholine.

(4) Each analgesic agent at various doses in the presence of AA, DGLA, or EPA.

(5) Botulinum neurotoxin A alone at various doses.

(6) Botulinum neurotoxin A at various doses in the presence of LPS.

(7) Botulinum neurotoxin A at various doses in the presence of carbachol or acetylcholine.

(8) Botulinum neurotoxin A at various doses in the presence of AA, DGLA, or EPA.

(9) Each antimuscarinic agent alone at various doses.

(10) Each antimuscarinic agent at various doses in the presence of LPS.

(11) Each antimuscarinic agent at various doses in the presence of carbachol or acetylcholine.

(12) Each antimuscarinic agent at various doses in the presence of AA, DGLA, or EPA.

[0219] The cells are then analyzed for the release of PGH_2, PGE, PGE_2, Prostacydin, Thromboxane, IL-1β, IL-6, TNF-α, the COX2 activity, the production of cAMP and cGMP, the production of IL-1β, IL-6, TNF-α and COX2 mRNA, and surface expression of CD80, CD86 and MHC class II molecules.

Materials and Methods

Isolation and purification of mouse bladder cells

[0220] Bladder cells were removed from euthanized animals C57BL/6 mice (8-12 weeks old) and cells were isolated by enzymatic digestion followed by purification on a Percoll gradient. Briefly, bladders from 10 mice were minced with scissors to fine slurry in 10 ml of digestion buffer (RPMI 1640, 2% fetal bovine serum, 0.5 mg/ml collagenase, 30

μg/ml DNase). Bladder slurries were enzymatically digested for 30 minutes at 37°C. Undigested fragments were further dispersed through a cell-trainer. The cell suspension was pelleted and added to a discontinue 20%, 40% and 75% Percoll gradient for purification on mononuclear cells. Each experiment used 50-60 bladders.

[0221] After washes in RPMI 1640, bladder cells were resuspended RPMI 1640 supplemented with 10 % fetal bovine serum, 15 mM HEPES, 2 mM L-glutamine, 100 U/ml penicillin, and 100 μg / ml of streptomycin and seeded in clear-bottom black 96-well cell culture microculture plates at a cell density of $3x10^4$ cells per well in 100 μl. Cells were cultured at 37° C in a 5 % CO_2 atmosphere.

***In vitro* treatment of cells with analgesics**

[0222] Bladder cells were treated with analgesic solutions (50 μl/ well) either alone or together with carbachol (10-Molar, 50 μl/ well), as an example of non-inflammatory stimuli, or lipopolysaccharide (LPS) of *Salmonella typhimurium* (1 μg/ml, 50 μl/ well), as an example of non-inflammatory stimuli. When no other effectors were added to the cells, 50 μl of RPMI 1640 without fetal bovine serum were added to the wells to adjust the final volume to 200 μl.

[0223] After 24 hours of culture, 150 μl of culture supernatants were collected, spun down for 2 min at 8,000 rpm at 4°C to remove cells and debris and stored at -70°C for analysis of Prostaglandin E2 (PGE_2) responses by ELISA. Cells were fixed, permeabilized and blocked for detection of Cyclooxygenase-2 (COX2) using a fluorogenic substrate. In selected experiment cells were stimulated 12 hours *in vitro* for analysis of COX2 responses

Analysis of COX2 responses

[0224] COX2 responses were analyzed by a Cell-Based ELISA using Human/mouse total COX2 immunoassay (R&D Systems), following the instructions of the manufacturer. Briefly, after cells fixation and permeabilization, a mouse anti-total COX2 and a rabbit anti-total GAPDH were added to the wells of the clear-bottom black 96-well cell culture microculture plates. After incubation and washes, an HRP-conjugated anti-mouse IgG and an AP-conjugated anti-rabbit IgG were added to the wells. Following another incubation and set of washes, the HRP- and AP-fluorogenic substrates were added. Finally, a Victor® V multilabel plate reader (PerkinElmer) was used to read the fluorescence emitted at 600 nm (COX2 fluorescence) and 450 nm (GAPDH fluorescence). Results are expressed as relative levels of total COX2 as determined by relative fluorescence unit (RFUs) and normalized to the housekeeping protein GAPDH.

Analysis of PGE2 responses

[0225] Prostaglandin E2 responses were analyzed by a sequential competitive ELISA (R&D Systems). More specifically, culture supernatants or PGE2 standards were added to the wells of a 96-well polystyrene microplate coated with a goat anti-mouse polyclonal antibody. After one hour incubation on a microplate shaker, an HRP-conjugated PGE2 was added and plates incubated for an additional two hours at room temperature. The plates were then washed and HRP substrate solution added to each well. The color was allowed to develop for 30 min and the reaction stopped by addition sulfuric acid before reading the plate at 450 nm with wavelength correction at 570 nm. Results are expressed as mean pg/ml of PGE2.

Other assays

[0226] The release of PGH_2, PGE, Prostacydin, Thromboxane, IL-1β, IL-6, and TNF-α, the production of cAMP and cGMP, the production of IL-1β, IL-6, TNF-α and COX2 mRNA, and surface expression of CD80, CD86 and MHC class II molecules are determined as described in Example 2.

Analgesics inhibit COX2 responses of mouse bladder cells to an inflammatory stimulus

[0227] Several analgesics (acetaminophen, aspirin, ibuprofen and naproxen) were tested on mouse bladder cells at the concentration of 5 μM or 50 μM to determine whether the analgesics could induce COX2 responses. Analysis of 24-hour cultures showed that none of the analgesics tested induced COX2 responses in mouse bladder cells *in vitro*.

[0228] The effect of these analgesics on the COX2 responses of mouse bladder cells to carbachol or LPS stimulation *in vitro* was also tested. As indicated in Table 1, the dose of carbachol tested has no significant effect on COX2 levels in mouse bladder cells. On the other hand, LPS significantly increased total COX2 levels. Interestingly, acetaminophen, aspirin, ibuprofen and naproxen could all suppress the effect of LPS on COX2 levels. The suppressive effect of the analgesic was seen when these drugs were tested at either 5 μM or 50 μM (Table 4).

Table 4. COX2 expression by mouse bladder cells after *in vitro* stimulation and treatment with analgesic

Stimulus	Analgesic	Total COX2 levels (Normalized RFUs)
None	None	158 ± 18
Carbachol (mM)	None	149 ± 21
LPS (1μg/ml)	None	420 ± 26
LPS (1μg/ml)	Acetaminophen (5 μM)	275 ± 12
LPS (1μg/ml)	Aspirin (5 μM)	240 ± 17
LPS (1μg/ml)	Ibuprofen (5 μM))	253 ± 32
LPS (1μg/ml)	Naproxen (5 μM)	284 ± 11
LPS (1μg/ml)	Acetaminophen (50 μM)	243 ± 15
LPS (1μg/ml)	Aspirin (50 μM)	258 ± 21
LPS (1μg/ml)	Ibuprofen (50 μM)	266 ± 19
LPS (1μg/ml)	Naproxen (50 μM)	279 ± 23

Analgesics inhibit PGE2 responses of mouse bladder cells to an inflammatory stimulus

[0229] The secretion of PGE2 in culture supernatants of mouse bladder cells was measured to determine the biological significance of the alteration of mouse bladder cell COX2 levels by analgesics. As shown in Table 5, PGE2 was not detected in the culture supernatants of unstimulated bladder cells or bladder cells cultured in the presence of carbachol. Consistent with COX2 responses described above, stimulation of mouse bladder cells with LPS induced the secretion of high levels of PGE2. Addition of the analgesics acetaminophen, aspirin, ibuprofen and naproxen suppressed the effect of LPS on PGE2 secretion and no difference was seen between the responses of cells treated with the 5 or 50 μM dose of analgesic.

Table 5. PGE2 secretion by mouse bladder cells after in vitro stimulation and treatment with analgesic.

Stimulus	Analgesic	PGE2 levels (pg/ml)
None	None	< 20.5
Carbachol (mM)	None	< 20.5
LPS (1μg/ml)	None	925 ± 55
LPS (1μg/ml)	Acetaminophen (5 μM)	619 ± 32
LPS (1μg/ml)	Aspirin (5 μM)	588 ± 21
LPS (1μg/ml)	Ibuprofen (5 μM))	593 ± 46
LPS (1μg/ml)	Naproxen (5 μM)	597± 19
LPS (1μg/ml)	Acetaminophen (50 μM)	600 ± 45
LPS (1μg/ml)	Aspirin (50 μM)	571 ± 53
LPS (1μg/ml)	Ibuprofen (50 μM)	568 ± 32
LPS (1μg/ml)	Naproxen (50 μM)	588 ± 37

[0230] In summary, these data show that the analgesics alone at 5 μM or 50 μM do not induce COX2 and PGE2 responses in mouse bladder cells. The analgesics at 5 μM or 50

μM, however, significantly inhibit COX2 and PGE2 responses of mouse bladder cells stimulated *in vitro* with LPS (1 μg/ml). No significant effect of analgesics was observed on COX2 and PGE2 responses of mouse bladder cells stimulated with carbachol (1 mM).

EXAMPLE 4: EFFECT OF ANALGESIC AGENTS, BOTULINUM NEUROTOXIN AND ANTIMUSCARINIC AGENTS ON MOUSE BLADDER SMOOTH MUSCLE CELL CONTRACTION.

Experimental Design

[0231] Cultured mouse or rat bladder smooth muscle cells and mouse or rat bladder smooth muscle tissue are exposed to inflammatory stimuli and non-inflammatory stimuli in the presence of analgesic agent and/or antimuscarinic agent at various concentrations. The stimuli-induced muscle contraction is measured to evaluate the inhibitory effect of the analgesic agent and/or antimuscarinic agent.

[0232] The effectors, analgesic agents and antimuscarinic agents are described in Example 2.

[0233] Primary cultures of mouse bladder smooth muscle cells are subjected to short term (1-2 hrs) or long term (24-48 hrs) stimulation with:

(1) Each analgesic agent alone at various doses.

(2) Each analgesic agent at various doses in the presence of LPS.

(3) Each analgesic agent at various doses in the presence of carbachol or acetylcholine.

(4) Each analgesic agent at various doses in the presence of AA, DGLA, or EPA.

(5) Botulinum neurotoxin A alone at various doses.

(6) Botulinum neurotoxin A at various doses in the presence of LPS.

(7) Botulinum neurotoxin A at various doses in the presence of carbachol or acetylcholine.

(8) Botulinum neurotoxin A at various doses in the presence of AA, DGLA, or EPA.

(9) Each antimuscarinic agent alone at various doses.

(10) Each antimuscarinic agent at various doses in the presence of LPS.

(11) Each antimuscarinic agent at various doses in the presence of carbachol or acetylcholine.

(12) Each antimuscarinic agent at various doses in the presence of AA, DGLA, or EPA.

Materials and Methods

[0234] Primary mouse bladder cells are isolated as described in Example 3. In selected experiments, cultures of bladder tissue are used. Bladder smooth muscle cell contractions are recorded with a Grass polygraph (Quincy Mass, USA).

EXAMPLE 5: EFFECT OF ORAL ANALGESIC AGENTS AND ANTIMUSCARINIC AGENTS ON COX2 AND PGE2 RESPONSES OF MOUSE BLADDER SMOOTH MUSCLE CELLS.

Experimental design:

[0235] Normal mice and mice with over active bladder syndrome are given oral doses of aspirin, naproxen sodium, ibuprofen, Indocin, nabumetone, Tylenol, Celecoxib, oxybutynin, solifenacin, darifenacin, atropine and combinations thereof. Control groups include untreated normal mice and untreated OAB mice with over active bladder syndrome. Thirty (30) minutes after last doses, the bladders are collected and stimulated *ex vivo* with carbachol or acetylcholine. In selected experiments, the bladders are treated with botulinum neurotoxin A before stimulation with carbachol. Animals are maintained in metabolic cages and frequency (and volume) of urination are evaluated. Bladder outputs are determined by monitoring water intake and cage litter weight. Serum PGH_2, PGE, PGE_2, Prostacydin, Thromboxane, IL-1β, IL-6, TNF-α, cAMP, and cGMP levels are determined by ELISA. CD80, CD86, MHC class II expression in whole blood cells are determined by flow cytometry.

[0236] At the end of the experiment, animals are euthanized and *ex vivo* bladder contractions are recorded with a Grass polygraph. Portions of bladders are fixed in formalin, and COX2 responses are analyzed by immunohistochemistry.

EXAMPLE 6: EFFECT OF ANALGESIC AGENTS, BOTULINUM NEUROTOXIN AND ANTIMUSCARINIC AGENTS ON HUMAN BLADDER SMOOTH MUSCLE CELL RESPONSES TO INFLAMMATORY AND NON-INFLAMMATORY STIMULI

Experimental Design

[0237] This study is designed to characterize how the optimal doses of analgesic determined in Examples 1-5 affect human bladder smooth muscle cells in cell culture or tissue cultures, and to address whether different classes of analgesics can synergize to more efficiently inhibit COX2 and PGE2 responses.

[0238] The effectors, analgesic agents and antimuscarinic agents are described in Example 2.

[0239] Human bladder smooth muscle cells are subjected to short term (1-2 hrs) or long term (24-48 hrs) stimulation with:

(1) Each analgesic agent alone at various doses.

(2) Each analgesic agent at various doses in the presence of LPS.

(3) Each analgesic agent at various doses in the presence of carbachol or acetylcholine.

(4) Each analgesic agent at various doses in the presence of AA, DGLA, or EPA.

(5) Botulinum neurotoxin A alone at various doses.

(6) Botulinum neurotoxin A at various doses in the presence of LPS.

(7) Botulinum neurotoxin A at various doses in the presence of carbachol or acetylcholine.

(8) Botulinum neurotoxin A at various doses in the presence of AA, DGLA, or EPA.

(9) Each antimuscarinic agent alone at various doses.

(10) Each antimuscarinic agent at various doses in the presence of LPS.

(11) Each antimuscarinic agent at various doses in the presence of carbachol or acetylcholine.

(12) Each antimuscarinic agent at various doses in the presence of AA, DGLA, or EPA.

[0240] The cells are then analyzed for the release of PGH_2, PGE, PGE_2, Prostacydin, Thromboxane, IL-1β, IL-6, TNF-α, the COX2 activity, the production of cAMP and cGMP, the production of IL-1β, IL-6, TNF-α and COX2 mRNA, and surface expression of CD80, CD86 and MHC class II molecules.

EXAMPLE 7: EFFECT OF ANALGESIC AGENTS, BOTULINUM NEUROTOXIN AND ANTIMUSCARINIC AGENTS ON HUMAN BLADDER SMOOTH MUSCLE CELL CONTRACTION.

Experimental Design

[0241] Cultured human bladder smooth muscle cells are exposed to inflammatory stimuli and non-inflammatory stimuli in the presence of an analgesic agent and/or antimuscarinic agent at various concentrations. The stimulus-induced muscle contraction is measured to evaluate the inhibitory effect of the analgesic agent and/or antimuscarinic agent.

[0242] The effectors, analgesic agents and antimuscarinic agents are described in Example 2.

[0243] Human bladder smooth muscle cells are subjected to short term (1-2 hrs) or long term (24-48 hrs) stimulation with:

(1) Each analgesic agent alone at various doses.

(2) Each analgesic agent at various doses in the presence of LPS.

(3) Each analgesic agent at various doses in the presence of carbachol or acetylcholine.

(4) Each analgesic agent at various doses in the presence of AA, DGLA, or EPA.

(5) Botulinum neurotoxin A alone at various doses.

(6) Botulinum neurotoxin A at various doses in the presence of LPS.

(7) Botulinum neurotoxin A at various doses in the presence of carbachol or acetylcholine.

(8) Botulinum neurotoxin A at various doses in the presence of AA, DGLA, or EPA.

(9) Each antimuscarinic agent alone at various doses.

(10) Each antimuscarinic agent at various doses in the presence of LPS.

(11) Each antimuscarinic agent at various doses in the presence of carbachol or acetylcholine.

(12) Each antimuscarinic agent at various doses in the presence of AA, DGLA, or EPA.

[0244] Bladder smooth muscle cell contractions are recorded with a Grass polygraph (Quincy Mass, USA).

EXAMPLE 8: EFFECT OF ANALGESIC AGENTS ON NORMAL HUMAN BLADDER SMOOTH MUSCLE CELL RESPONSES TO INFLAMMATORY AND NON INFLAMMATORY SIGNALS

EXPERIMENTAL DESIGN

Culture of normal human bladder smooth muscle cells

[0245] Normal human bladder smooth muscle cells were isolated by enzymatic digestion from macroscopically normal pieces of human bladder. Cells were expended *in vitro* by culture at 37° C in a 5 % CO_2 atmosphere in RPMI 1640 supplemented with 10 % fetal bovine serum, 15 mM HEPES, 2 mM L-glutamine, 100 U/ml penicillin, and 100 mg / ml of streptomycin and passage once a week by treatment with trypsin to detach cells followed by reseeding in a new culture flask. The first week of culture, the culture medium was supplemented with 0.5 ng/ml epidermal growth factor, 2 ng/ml fibroblast growth factor, and 5 μg/ml insulin.

Treatment of normal human bladder smooth muscle cells with analgesics *in vitro*

[0246] Bladder smooth muscle cells trypsinized and seeded in microculture plates at a cell density of $3x10^4$ cells per well in 100 µl were treated with analgesic solutions (50 µl/ well) either alone or together carbachol (10-Molar, 50 µl/ well), as an example of non-inflammatory stimuli, or lipopolysaccharide (LPS) of *Salmonella typhimurium* (1 µg/ml, 50 µl/ well), as an example of non-inflammatory stimuli. When no other effectors were added to the cells, 50 µl of RPMI 1640 without fetal bovine serum were added to the wells to adjust the final volume to 200 µl.

[0247] After 24 hours of culture, 150 µl of culture supernatants were collected, spun down for 2 min at 8,000 rpm at 4°C to remove cells and debris and stored at -70°C for analysis of Prostaglandin E2 (PGE_2) responses by ELISA. Cells were fixed, permeabilized and blocked for detection of COX2 using a fluorogenic substrate. In selected experiment cells were stimulated 12 hours *in vitro* for analysis of COX2, PGE2 and cytokine responses.

Analysis of COX2, PGE2 and cytokine responses

[0248] COX2 and PGE2 responses were analyzed as described in Example 3. Cytokine responses were analyzed as described in Example 2.

RESULTS

[0249] *Analgesics inhibit COX2 responses of normal human bladder smooth muscle cells to inflammatory and non- inflammatory stimuli* - Analysis of cells and culture supernatants after 24 hours of cultures showed that none of the analgesics tested alone induced COX2 responses in normal human bladder smooth muscle cells. However, as summarized in Table 6, carbachol induced low, but significant COX2 responses in normal human bladder smooth muscle cells. On the other hand, LPS treatment resulted in higher levels of COX2 responses in normal human bladder smooth muscle cells. Acetaminophen, aspirin, ibuprofen and naproxen could all suppress the effect of carbachol and LPS on COX2 levels. The suppressive effect of the analgesics was seen on LPS-induced responses when these drugs were tested at either 5 µM or 50 µM.

Table 6. COX2 expression by normal human bladder smooth muscle cells after *in vitro* stimulation with inflammatory and non- inflammatory stimuli and treatment with analgesic

Stimulus	**Analgesic**	**Total COX2 levels[#] (Normalized RFUs) subject 1**	**Total COX2 levels (Normalized RFUs) subject 2**
None	None	230	199
Carbachol 10^{-3} M	None (50 μM)	437	462
Carbachol 10^{-3} M	Acetaminophen (50 μM)	298	310
Carbachol 10^{-3} M	Aspirin (50 μM)	312	297
Carbachol 10^{-3} M	Ibuprofen (50 μM)	309	330
Carbachol 10^{-3} M	Naproxen (50 μM)	296	354
LPS (10 μg/ml)	None	672	633
LPS (10 μg/ml)	Acetaminophen (5 μM)	428	457
LPS (10 μg/ml)	Aspirin (5 μM)	472	491
LPS (10 μg/ml)	Ibuprofen (5 μM)	417	456
LPS (10 μg/ml)	Naproxen (5 μM	458	501
LPS (10 μg/ml)	Acetaminophen (50 μM)	399	509
LPS (10 μg/ml)	Aspirin (50 μM)	413	484
LPS (10 μg/ml)	Ibuprofen (50 μM)	427	466
LPS (10 μg/ml)	Naproxen (50 μM)	409	458

[#]Data are expressed as mean of duplicates

[0250] *Analgesics inhibit PGE2 responses of normal human bladder smooth muscle cells to inflammatory and non- inflammatory stimuli* - Consistent with the induction of COX2 responses described above, both carbachol and LPS induced production of PGE2 by normal human bladder smooth muscle cells. Acetaminophen, aspirin, ibuprofen and naproxen were also found to suppress the LPS-induced PGE2 responses at either 5 μM or 50 μM (Table 7).

Table 7. PGE2 secretion by normal human bladder smooth muscle cells after in vitro stimulation with inflammatory and non- inflammatory stimuli and treatment with analgesic

Stimulus	**Analgesic**	**PGE2 levels[#] (pg/ml) Subject 1**	**PGE2 levels (pg/ml) Subject 2**
None	None	< 20.5	< 20.5
Carbachol 10^{-3} M	None	129	104
Carbachol 10^{-3} M	Acetaminophen (50 μM)	76	62
Carbachol 10^{-3} M	Aspirin (50 μM)	89	59
Carbachol 10^{-3} M	Ibuprofen (50 μM)	84	73
Carbachol 10^{-3} M	Naproxen (50 μM)	77	66
LPS (10 μg/ml)	None	1125	998
LPS (10 μg/ml)	Acetaminophen (5 μM)	817	542
LPS (10 μg/ml)	Aspirin (5 μM)	838	598
LPS (10 μg/ml)	Ibuprofen (5 μM)	824	527
LPS (10 μg/ml)	Naproxen (5 μM	859	506
LPS (10 μg/ml)	Acetaminophen (50 μM)	803	540
LPS (10 μg/ml)	Aspirin (50 μM)	812	534
LPS (10 μg/ml)	Ibuprofen (50 μM)	821	501
LPS (10 μg/ml)	Naproxen (50 μM)	819	523

[#]Data are expressed as mean of duplicates

[0251] *Analgesics inhibit cytokine responses of normal human bladder cells to inflammatory stimuli* - Analysis of cells and culture supernatants after 24 hours of culture showed that none of the analgesics tested alone induced IL-6 or TNFα secretion in normal human bladder smooth muscle cells. As shown in Tables 8 and 9, the doses of carbachol tested induced low, but significant TNFα and IL-6 responses in normal human bladder smooth muscle cells. On the other hand, LPS treatment resulted in massive induction of these proinflammatory cytokines. Acetaminophen, aspirin, ibuprofen and naproxen suppress the effect of carbachol and LPS on TNFα and IL-6 responses. The suppressive effect of the analgesics on LPS-induced responses was seen when these drugs were tested at either 5 μM or 50 μM.

Table 8. TNFα secretion by normal human bladder smooth muscle cells after in vitro stimulation with inflammatory and non- inflammatory stimuli and treatment with analgesic

Stimulus	**Analgesic**	**TNFα (pg/ml) [#] Subject 1**	**TNFα (pg/ml) Subject 2**
None	None	< 5	< 5
Carbachol 10^{-3} M	None	350	286
Carbachol 10^{-3} M	Acetaminophen (50 μM)	138	164
Carbachol 10^{-3} M	Aspirin (50 μM)	110	142
Carbachol 10^{-3} M	Ibuprofen (50 μM)	146	121
Carbachol 10^{-3} M	Naproxen (50 μM)	129	137
LPS (10 μg/ml)	None	5725	4107
LPS (10 μg/ml)	Acetaminophen (5 μM)	2338	2267
LPS (10 μg/ml)	Aspirin (5 μM)	2479	2187
LPS (10 μg/ml)	Ibuprofen (5 μM)	2733	2288
LPS (10 μg/ml)	Naproxen (5 μM	2591	2215
LPS (10 μg/ml)	Acetaminophen (50 μM)	2184	2056
LPS (10 μg/ml)	Aspirin (50 μM)	2266	2089
LPS (10 μg/ml)	Ibuprofen (50 μM)	2603	1997
LPS (10 μg/ml)	Naproxen (50 μM)	2427	2192

[#]Data are expressed as mean of duplicates.

Table 9. IL-6 secretion by normal human bladder smooth muscle cells after in vitro stimulation with inflammatory and non- inflammatory stimuli and treatment with analgesic

Stimulus	**Analgesic**	**IL-6 (pg/ml) [#] Subject 1**	**IL-6 (pg/ml) Subject 2**
None	None	< 5	< 5
Carbachol 10^{-3}M	None	232	278
Carbachol 10^{-3} M	Acetaminophen (50 μM)	119	135
Carbachol 10^{-3} M	Aspirin (50 μM)	95	146
Carbachol 10^{-3} M	Ibuprofen (50 μM)	107	118
Carbachol 10^{-3} M	Naproxen (50 μM)	114	127
LPS (10 μg/ml)	None	4838	4383
LPS (10 μg/ml)	Acetaminophen (5 μM)	2012	2308
LPS (10 μg/ml)	Aspirin (5 μM)	2199	2089
LPS (10 μg/ml)	Ibuprofen (5 μM)	2063	2173
LPS (10 μg/ml)	Naproxen (5 μM	2077	2229
LPS (10 μg/ml)	Acetaminophen (50 μM)	2018	1983
LPS (10 μg/ml)	Aspirin (50 μM)	1987	2010
LPS (10 μg/ml)	Ibuprofen (50 μM)	2021	1991
LPS (10 μg/ml)	Naproxen (50 μM)	2102	2028

[#]Data are expressed as mean of duplicates.

[0252] Primary normal human bladder smooth muscle cells were isolated, cultured and evaluated for their responses to analgesics in the presence of non-inflammatory (carbachol) and inflammatory (LPS) stimuli. The goal of this study was to determine

whether or not normal human bladder smooth muscle cells recapitulate the observations previously made with murine bladder cells.

[0253] The above-described experiment will be repeated with analgesic agents and/or antimuscarinic agents in delayed-release, or extended-release formulation or delayed-and-extended-release formulations.

[0254] The above description is for the purpose of teaching the person of ordinary skill in the art how to practice the present invention, and it is not intended to detail all those obvious modifications and variations of it which will become apparent to the skilled worker upon reading the description. It is intended, however, that all such obvious modifications and variations be included within the scope of the present invention, which is defined by the following claims. The claims are intended to cover the claimed components and steps in any sequence which is effective to meet the objectives there intended, unless the context specifically indicates the contrary.

WHAT IS CLAIMED IS:

1. A method for reducing the frequency of urination, comprising:

administering to a subject in need thereof a pharmaceutical composition comprising:

one or more analgesic agents; and

one or more additional active ingredients selected from the group consisting of α-blockers and 5α-reductase inhibitors.

2. The method of Claim 1, wherein said one or more analgesic agents and said one or more additional active ingredients are formulated for immediate release. 3. The method of Claim 1, wherein said one or more analgesic agents and said one or more additional active ingredients are formulated for delayed release.

4. The method of Claim 1, wherein said one or more analgesic agents and said one or more additional active ingredients are formulated for extended release.

5. The method of Claim 4, wherein said one or more analgesic agents are administered

in an amount of 50-400 mg per agent, wherein said one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen, and wherein said pharmaceutical composition is formulated for extended-release such that said one or more analgesic agents and said one or more additional active ingredients are released continuously over a period of 5-24 hours.

6. The method of Claim 5, wherein said one or more additional active ingredients comprise tamsulosin.

7. The method of Claim 5, wherein said one or more additional active ingredients comprise finasteride.

8. The method of Claim 5, wherein said one or more additional active ingredients comprise tamsulosin and finasteride.

9. The method of Claim 4, wherein said one or more analgesic agents are administered

in an amount of 50-400 mg per agent, wherein said one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen, and wherein said pharmaceutical composition is formulated for extended release, characterized by a two-phase release profile in which 20-60% of said one or more analgesic agents are released within two hours of administration and remainder of said one or more analgesic agents are released continuously over a period of 5-24 hours.

10. The method of Claim 9, wherein said one or more additional active ingredients comprise tamsulosin.

11. The method of Claim 9, wherein said one or more additional active ingredients comprise finasteride.

12. The method of Claim 9, wherein said one or more additional active ingredients comprise tamsulosin and finasteride.

13. The method of Claim 1, wherein said one or more analgesic agents are formulated for extended release and said one or more additional active ingredients are formulated for immediate release.

14. The method of Claim 13, wherein said one or more analgesic agents are administered

in an amount of 50-400 mg per agent, wherein said one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen, and wherein said one or more analgesic agents are formulated for extended-release such that said one or more analgesic agents are released continuously over a period of 5-24 hours.

15. The method of Claim 14, wherein said one or more additional active ingredients comprise tamsulosin.

16. The method of Claim 14, wherein said one or more additional active ingredients comprise finasteride.

17. The method of Claim 14, wherein said one or more additional active ingredients comprise tamsulosin and finasteride.

18. The method of Claim 13, wherein said one or more analgesic agents are administered

in an amount of 50-400 mg per agent, wherein said one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen, and wherein said one or more analgesic agents are formulated for extended release, characterized by a two-phase release profile in which 20-60% of said one or more analgesic agents are released within two hours of administration and remainder of said one or more analgesic agents are released continuously over a period of 5-24 hours.

19. The method of Claim 18, wherein said one or more additional active ingredients comprise tamsulosin.

20. The method of Claim 18, wherein said one or more additional active ingredients comprise finasteride.

21. The method of Claim 18, wherein said one or more additional active ingredients comprise tamsulosin and finasteride.

22. The method of Claim 1, wherein said pharmaceutical composition further comprises an antimuscarinic agent.

23. The method of Claim 1, wherein said pharmaceutical composition further comprises an antidiuretic agent.

24. The method of Claim 1, wherein said pharmaceutical composition further comprises a spasmolytic.

25. The method of Claim 1, further comprising the step of administering an effective amount of a diuretic prior to the administration of said pharmaceutical composition, wherein said diuretic is administered 7 or 8 hours prior to bedtime.

26. The method of Claim 1, wherein said subject is a mammal.

27. A pharmaceutical composition for reducing frequency of urination, comprising:

one or more analgesic agents;

one or more α-blockers, and

a pharmaceutically acceptable carrier'

wherein said one or more analgesic agents are formulated for extended release and wherein said one or more α-blockers are formulated for immediate release.

28. The pharmaceutical composition of Claim 27, comprising one or more analgesic agents in an amount of 50-400 mg per agent, wherein said one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen, and wherein said one or more analgesic agents are formulated for extended-release such that said one or more analgesic agents are released continuously over a period of 5-24 hours.

29. The pharmaceutical composition of Claim 28, wherein said one or more analgesic agents comprise acetaminophen and wherein said one or more α-blockers comprise tamsulosin.

30. The pharmaceutical composition of Claim 27, comprising one or more analgesic agents in an amount of 50-400 mg per agent, wherein said one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen, and wherein said pharmaceutical composition is formulated for extended release, characterized by a two-phase release profile

in which 20-60% of said one or more analgesic agents are released within two hours of administration and remainder of said one or more analgesic agents are released continuously over a period of 5-24 hours.

31. The pharmaceutical composition of Claim 30, wherein said one or more analgesic agents comprise acetaminophen and wherein said one or more α-blockers comprise tamsulosin.

32. A pharmaceutical composition for reducing frequency of urination, comprising:

one or more analgesic agents;

one or more 5α-reductase inhibitors, and

a pharmaceutically acceptable carrier

wherein said one or more analgesic agents are formulated for extended release and wherein said one or more 5α-reductase inhibitors are formulated for immediate release.

33. The pharmaceutical composition of Claim 32, comprising one or more analgesic agents in an amount of 50-400 mg per agent, wherein said one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen, and wherein said one or more analgesic agents are formulated for extended-release such that said one or more analgesic agents are released continuously over a period of 5-24 hours.

34. The pharmaceutical composition of Claim 33, wherein said one or more analgesic agents comprise acetaminophen and wherein said one or more 5α-reductase inhibitors comprise finasteride.

35. The pharmaceutical composition of Claim 32, comprising one or more analgesic agents in an amount of 50-400 mg per agent, wherein said one or more analgesic agents are selected from the group consisting of aspirin, ibuprofen, naproxen, naproxen sodium, indomethacin, nabumetone, and acetaminophen, and wherein said pharmaceutical composition is formulated for extended release, characterized by a two-phase release profile in which 20-60% of said one or more analgesic agents are released within two hours of administration and remainder of said one or more analgesic agents are released continuously over a period of 5-24 hours.

36. The pharmaceutical composition of Claim 35, wherein said one or more analgesic agents comprise acetaminophen and wherein said one or more 5α-reductase inhibitors comprise finasteride.

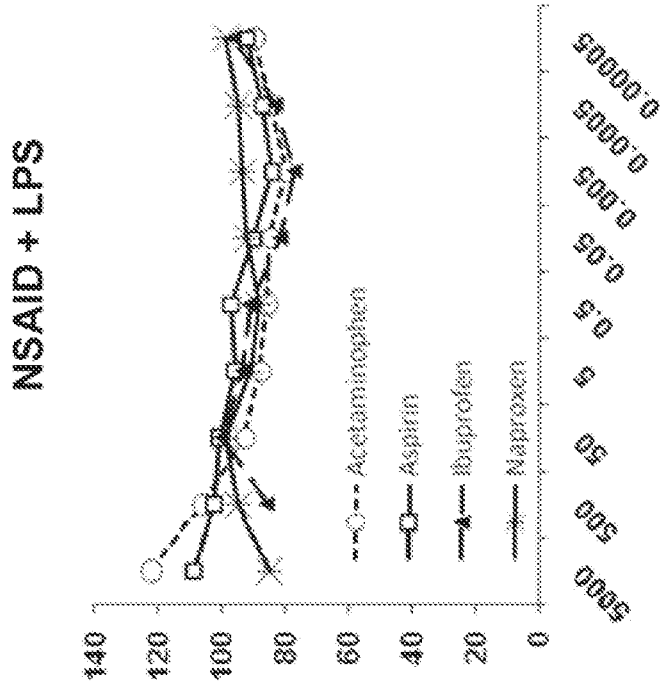
NSAID + LPS
CD40+CD80+ cells
(Percent of control without NSAID
140
120
100
80
60
40
20
0
5000
500
50
5
0.5
0.05
0.005
0.0005
0.00005
Dose of NSAID
(5000-0.00005 μM)
Acetaminophen
Aspirin
Ibuprofen
Naproxen

FIG. 1B

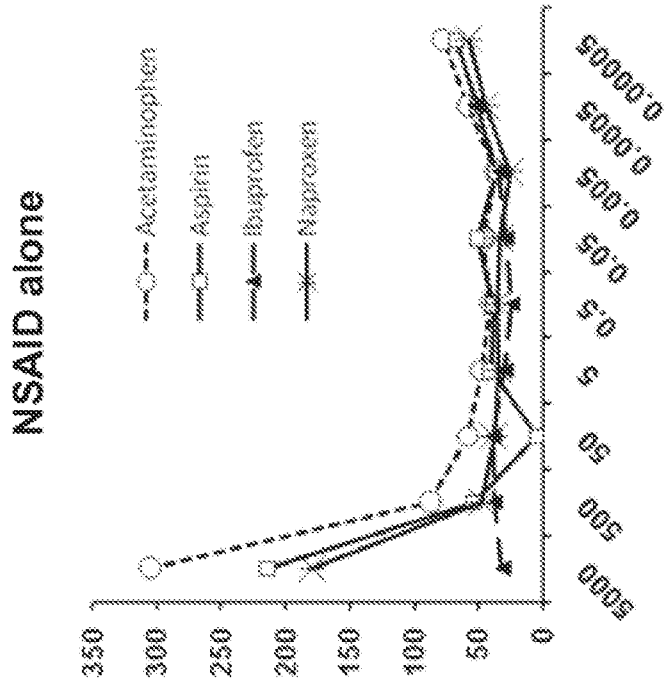
NSAID alone
CD40+CD80+ cells
(Percent of control without NSAID
350
300
250
200
150
100
50
0
5000
500
50
5
0.5
0.05
0.005
0.0005
0.00005
Dose of NSAID
(5000-0.00005 μM)
Acetaminophen
Aspirin
Ibuprofen
Naproxen

FIG. 1A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/031617

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/192(2006.01)i, A61K 31/19(2006.01)i, A61P 7/12(2006.01)i, A61P 7/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/192; A61K 31/4178; A61K 31/137; A61P 13/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: antimuscarinic agent, overactive bladder, analgesic agent, alpha-blocker, 5alpha-reductase inhibitor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7678821 B2 (PABORJI, M.) 16 March 2010 See abstract; columns 1-3 and 8-11; and claims 1-13.	27-36
A	US 2012-0010294 A1 (DILL, D. A.) 12 January 2012 See abstract; paragraphs [0008]-[0060]; and claims 1-20.	27-36
A	KAPLAN, S. A. et al., `Urinary retention and post-void residual urine in men: separating truth from tradition`, The Journal of Urology, 2008, Vol. 180, pages 47-54. See pages 47, 48, 51 and 52.	27-36
A	SONG, Y. S. et al., `Zolpidem pharmacotherapy combined with alpha-blocker therapy for nocturia unresponsive to alpha-blocker monotherapy in men with lower urinary tract symptoms: a preliminary study`, International Urology and Nephrology, 2007, Vol. 39, pages 1147-1152. See pages 1147-1149.	27-36
A	ROBINSON, D. et al., `A randomized double-blind placebo-controlled multicentre study to explore the efficacy and safety of tamsulosin and tolterodine in women with overactive bladder syndrome`, BJU International, 2007, Vol. 100, pages 840-845. See pages 840-844.	27-36

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2013 (24.06.2013)	**25 June 2013 (25.06.2013)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
CHOI, Sung Hee
Telephone No. 82-42-481-8740

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/031617

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-26
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-26 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/031617

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 7678821 B2	16.03.2010	AT 506059 T	15.05.2011
		AU 2006-284940 A1	08.03.2007
		AU 2006-284940 B2	22.03.2012
		BR PI0615432 A2	17.05.2011
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		EP 1933833 B8	14.09.2011
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		PT 1933833 E	08.07.2011
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		US 2010-0137392 A1	03.06.2010
		US 2010-0152263 A1	17.06.2010
		US 7781472 B2	24.08.2010
		WO 2007-027675 A1	08.03.2007
		ZA 200802811 A	30.09.2009
US 2012-0010294 A1	12.01.2012	WO 2012-005745 A2	12.01.2012

(19)中华人民共和国国家知识产权局

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2014.09.18

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代理人 朱梅 徐琳

(51)Int.Cl.
A61K 31/192(2006.01)
A61K 31/19(2006.01)
A61P 7/12(2006.01)
A61P 7/00(2006.01)

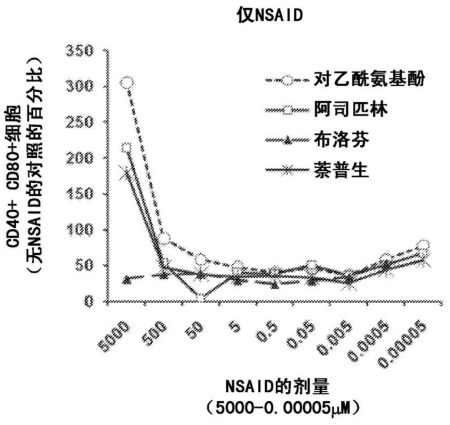
权利要求书3页 说明书47页 附图1页

(54)发明名称

用于缓解尿频的延长释放制剂及其使用方法

(57)摘要

本申请公开了一种缓解尿频的方法。所述方法包括向需要其的受试者施用有效量的药物组合物,所述药物组合物包含一种或多种镇痛剂和一种或多种 α-阻滞剂。在一个实施方式中,所述一种或多种镇痛剂被配制成延长释放。



CN 104321056 A

1. 一种缓解尿频的方法，其包括：

向需要其的受试者施用一种药物组合物，所述药物组合物包含：

一种或多种镇痛剂；和

一种或多种选自 α - 阻滞剂和 5α - 还原酶抑制剂的附加活性成分。

2. 根据权利要求 1 所述的方法，其中，所述一种或多种镇痛剂和所述一种或多种附加活性成分被配制成立即释放。

3. 根据权利要求 1 所述的方法，其中，所述一种或多种镇痛剂和所述一种或多种附加活性成分被配制成延迟释放。

4. 根据权利要求 1 所述的方法，其中，所述一种或多种镇痛剂和所述一种或多种附加活性成分被配制成延长释放。

5. 根据权利要求 4 所述的方法，其中，所述一种或多种镇痛剂以每剂 50-400mg 的量施用，其中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚，以及其中，所述药物组合物被配制成延长释放，使得所述一种或多种镇痛剂和所述一种或多种附加活性成分在 5-24 小时的时段内被连续释放。

6. 根据权利要求 5 所述的方法，其中，所述一种或多种附加活性成分包含坦洛新。

7. 根据权利要求 5 所述的方法，其中，所述一种或多种附加活性成分包含非那雄胺。

8. 根据权利要求 5 所述的方法，其中，所述一种或多种附加活性成分包含坦洛新和非那雄胺。

9. 根据权利要求 4 所述的方法，其中，所述一种或多种镇痛剂以每剂 50-400mg 的量施用，其中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚，以及其中，所述药物组合物被配制成以两段释放曲线为特点的延长释放，在该释放曲线中，所述一种或多种镇痛剂的 20-60％在施用 2 小时内释放，而所述一种或多种镇痛剂的剩余部分在 5-24 小时的时段内被连续释放。

10. 根据权利要求 9 所述的方法，其中，所述一种或多种附加活性成分包含坦洛新。

11. 根据权利要求 9 所述的方法，其中，所述一种或多种附加活性成分包含非那雄胺。

12. 根据权利要求 9 所述的方法，其中，所述一种或多种附加活性成分包含坦洛新和非那雄胺。

13. 根据权利要求 1 所述的方法，其中，所述一种或多种镇痛剂被配制成延长释放，而所述一种或多种附加活性成分被配制成立即释放。

14. 根据权利要求 13 所述的方法，其中，所述一种或多种镇痛剂以每剂 50-400mg 的量施用，其中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚，以及其中，所述一种或多种镇痛剂被配制成延长释放，使得所述一种或多种镇痛剂在 5-24 小时的时段内被连续释放。

15. 根据权利要求 14 所述的方法，其中，所述一种或多种附加活性成分包含坦洛新。

16. 根据权利要求 14 所述的方法，其中，所述一种或多种附加活性成分包含非那雄胺。

17. 根据权利要求 14 所述的方法，其中，所述一种或多种附加活性成分包含坦洛新和非那雄胺。

18. 根据权利要求 13 所述的方法，其中，所述一种或多种镇痛剂以每剂 50-400mg 的量施用，其中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘

丁美酮和对乙酰氨基酚，以及其中，所述一种或多种镇痛剂被配制成以两段释放曲线为特点的延长释放，在该释放曲线中，所述一种或多种镇痛剂的 20-60％在施用 2 小时内释放，而所述一种或多种镇痛剂的剩余部分在 5-24 小时的时段内被连续释放。

19. 根据权利要求 18 所述的方法，其中，所述一种或多种附加活性成分包含坦洛新。

20. 根据权利要求 18 所述的方法，其中，所述一种或多种附加活性成分包含非那雄胺。

21. 根据权利要求 18 所述的方法，其中，所述一种或多种附加活性成分包含坦洛新和非那雄胺。

22. 根据权利要求 1 所述的方法，其中，所述药物组合物进一步包含抗毒蕈碱剂。

23. 根据权利要求 1 所述的方法，其中，所述药物组合物进一步包含抗利尿剂。

24. 根据权利要求 1 所述的方法，其中，所述药物组合物进一步包含解痉剂。

25. 根据权利要求 1 所述的方法，进一步包括在施用所述药物组合物之前施用有效量的利尿剂的步骤，其中，所述利尿剂在睡前 7 或 8 小时施用。

26. 根据权利要求 1 所述的方法，其中，所述受试者为哺乳动物。

27. 一种缓解尿频的药物组合物，其包含：

一种或多种镇痛剂；

一种或多种 α－阻滞剂；和

药学上可接受的载体，

其中，所述一种或多种镇痛剂被配制成延长释放，以及其中，所述一种或多种 α－阻滞剂被配制成立即释放。

28. 根据权利要求 27 所述的药物组合物，其以每剂 50-400mg 的量包含一种或多种镇痛剂，其中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚，以及其中，所述一种或多种镇痛剂被配制成延长释放，使得所述一种或多种镇痛剂在 5-24 小时的时段内被连续释放。

29. 根据权利要求 28 所述的药物组合物，其中，所述一种或多种镇痛剂包含对乙酰氨基酚，以及其中，所述一种或多种 α－阻滞剂包含坦洛新。

30. 根据权利要求 27 所述的药物组合物，其以每剂 50-400mg 的量包含一种或多种镇痛剂，其中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚，以及其中，所述药物组合物被配制成以两段释放曲线为特点的延长释放，在该释放曲线中，所述一种或多种镇痛剂的 20-60％在施用 2 小时内释放，而所述一种或多种镇痛剂的剩余部分在 5-24 小时的时段内被连续释放。

31. 根据权利要求 30 所述的药物组合物，其中，所述一种或多种镇痛剂包含对乙酰氨基酚，以及其中，所述一种或多种 α－阻滞剂包含坦洛新。

32. 一种缓解尿频的药物组合物，其包含：

一种或多种镇痛剂；

一种或多种 5α－还原酶抑制剂；和

药学上可接受的载体，

其中，所述一种或多种镇痛剂被配制成延长释放，以及其中，所述一种或多种 5α－还原酶抑制剂被配制成立即释放。

33. 根据权利要求 32 所述的药物组合物，其以每剂 50-400mg 的量包含一种或多种镇痛

剂，其中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚，以及其中，所述一种或多种镇痛剂被配制成延长释放，使得所述一种或多种镇痛剂在 5-24 小时的时段内被连续释放。

34. 根据权利要求 33 所述的药物组合物，其中，所述一种或多种镇痛剂包含对乙酰氨基酚，以及其中，所述一种或多种 5α－还原酶抑制剂包括非那雄胺。

35. 根据权利要求 32 所述的药物组合物，其以每剂 50-400mg 的量包含一种或多种镇痛剂，其中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚，以及所述药物组合物被配制成以两段释放曲线为特点的延长释放，在该释放曲线中，所述一种或多种镇痛剂的 20-60％在施用 2 小时内释放，而所述一种或多种镇痛剂的剩余部分在 5-24 小时的时段内被连续释放。

36. 根据权利要求 35 所述的药物组合物，其中，所述一种或多种镇痛剂包含对乙酰氨基酚，以及其中，所述一种或多种 5α－还原酶抑制剂包含非那雄胺。

用于缓解尿频的延长释放制剂及其使用方法

[0001] 本申请要求享有在2012年6月4日提交的序号为13/487,348的美国专利申请和在2012年3月19日提交的序号为13/424,000的美国专利申请的优先权。

技术领域

[0002] 本申请主要涉及用于抑制肌肉收缩的方法和组合物，特别地，涉及用于抑制膀胱平滑肌收缩的方法和组合物。

背景技术

[0003] 逼尿肌是膀胱壁的一层，它是由以螺旋纤维束、纵向纤维束和环状纤维束排列的平滑肌纤维形成的。当膀胱被拉伸时，这会向副交感神经系统发信号收缩逼尿肌。这样促进膀胱通过尿道排尿。

[0004] 为了使尿排出膀胱，自主控制的内括约肌和随意控制的外括约肌都必须是开放的。这些肌肉出现问题可能会导致失禁。如果尿量达到膀胱的绝对容量的100％，随意括约肌便变为非随意的，而尿会被立即排出。

[0005] 成人的膀胱通常容纳大约300-350ml的尿（工作容积），但根据个体的不同，一个充满的成人膀胱可能容纳高达大约1000ml（绝对容积）。当尿蓄积时，由膀胱壁的折叠（褶皱）而形成的脊变平，并且膀胱壁随着它的拉伸而变薄，从而允许膀胱在内部压力没有显著升高的情况下储存更大量的尿。

[0006] 对于大多数个体来说，排尿的需求通常在膀胱内尿的体积达到大约200ml时开始。在这个阶段，如果个体需要，他很容易抑制排尿的冲动。随着膀胱持续充满，排尿的需求变得越来越强并且越来越难以忽视。最后，膀胱将充满到排尿的冲动无法抵抗的程度，从而个体将无法再忽视它。在某些个体中，这种排尿需求在膀胱与其工作容积相比小于100％充满时即可产生。这种增强的排尿需求可能会干扰正常活动，包括提供休息中充足的不间断睡眠的能力。在一些情况下，这种增强的排尿需求可能与内科状况有关，如男性良性前列腺增生或前列腺癌，或者女性妊娠。然而，增强的排尿需求也发生在没有被其他内科状况所影响的个体（男性和女性）中。

[0007] 因此，需要对于遭受膀胱与其工作容积相比小于100％充满尿时产生排尿需求困扰的男性或女性个体进行治疗的组合物和方法。所述组合物和方法被需要用于抑制肌肉收缩，从而允许在膀胱中尿体积超过大约工作容积的100％时所述个体的排尿需求开始。

发明内容

[0008] 本申请的一个方面涉及一种缓解受试者尿频的方法。所述方法包括向需要的受试者施用有效量的一种或多种镇痛剂和有效量的一种或多种选自α-阻滞剂和5α-还原酶抑制剂的附加活性成分。所述方法可以用于治疗夜尿症或活动过度的膀胱。

[0009] 本申请的另一个方面涉及一种药物组合物，所述药物组合物包含：包括一种或多种镇痛剂的活性成分，α-阻滞剂，和药学上可接受的载体。

[0010] 本申请的另一个方面涉及一种药物组合物，所述药物组合物包含：包括一种或多种镇痛剂的活性成分，5α－还原酶抑制剂，和药学上可接受的载体。

附图说明

[0011] 图1A和图1B是显示在缺少LPS(图1A)或存在LPS(图1B)的情况下，镇痛剂调节Raw 264巨噬细胞的辅刺激分子的表达的图。细胞在镇痛剂单独存在或与鼠伤寒沙门氏菌(Salmonella typhimurium)LPS(0.05μg/ml)共同存在下培养24小时。结果为CD40+CD80+细胞的平均相对百分比。

具体实施方式

[0012] 提出以下的详细说明以使本领域的技术人员实施和使用本发明。为了解释的目的，以下阐述具体术语以充分理解本发明。然而，对于本领域的技术人员来说，显然这些具体的细节在本发明实施中并不需要。提供具体应用的描述仅用作典型的实施例。本发明并不意欲限于所示的实施方式，而是希望包括与在此公开的原理和特征相一致的可能的最宽范围。

[0013] 在此使用的术语“有效量”是指达到被选定的结果所需的量。

[0014] 在此使用的术语“镇痛剂”是指用于缓解疼痛且包括抗炎化合物的试剂、化合物或药物。示例性的镇痛和/或抗炎的试剂、化合物或药物包括，但不限于下列物质：非甾体抗炎药物(NSAIDs)，水杨酸盐，阿司匹林，水杨酸，水杨酸甲酯，二氟尼柳，双水杨酯，奥沙拉嗪，柳氮磺吡啶，对氨基苯酚衍生物，乙酰苯胺，对乙酰氨基酚，非那西汀，灭酸酯，甲灭酸，甲氯灭酸酯，甲氯灭酸钠，杂芳基乙酸衍生物，托美汀，酮咯酸，双氯芬酸，丙酸衍生物，布洛芬，萘普生钠，萘普生，非诺洛芬，酮基布洛芬，氟比洛芬，奥沙普秦；烯醇酸，昔康衍生物，吡罗昔康，美洛昔康，替诺昔康，安吡昔康，屈噁昔康，匹伏昔康，吡唑酮衍生物，保泰松，羟基保泰松，安替比林，氨基比林，安乃近，考昔类药物(coxibs)，塞来考昔，罗非考昔，萘丁美酮，阿扎丙宗，吲哚美辛，舒林酸，依托度酸，异丁基苯基丙酸，鲁米考昔(lumiracoxib)，艾托考昔，帕瑞考昔，伐地考昔，替拉考昔(tiracoxib)，依托度酸，达布非酮，右酮洛芬，醋氯芬酸，利克飞龙(licofelone)，溴芬酸，氯索洛芬，吡喃洛芬，吡罗昔康，尼美舒利，西唑来汀，3-甲酰基氨基-7-甲基磺酰基氨基-6-苯氧基-4H-1-苯并吡喃-4-酮，美洛昔康，氯诺昔康，右旋吲哚布芬，莫苯唑酸，呱氨托美丁(amtolmetin)，普拉洛芬，托芬那酸，氟比洛芬，舒洛芬，奥沙普秦，扎托洛芬，阿明洛芬，噻洛芬酸，其药用盐，其水合物和其溶剂合物。

[0015] 在此使用的术语“考昔(coxib)”和“COX抑制剂”是指含有能够抑制COX2酶的活性或表达或者能够抑制或缓解严重的炎症反应的的严重程度(包括疼痛和肿胀)的化合物的组合物。

[0016] 在此使用的术语“衍生物”是指一种经化学修饰的化合物，该修饰被普通熟练的化学工作者认为是常规的途径，例如酸的酯或酰胺，保护基，例如针对醇或硫醇的苄基以及对于胺的叔丁氧基羰基基团。

[0017] 在此使用的术语“类似物”是指一种包括一个特定化合物或其类的化学修饰形式的化合物，该化合物保持所述特定化合物或其类的药物学和/或药理学活性特征。

[0018] 在此使用的“受试者”或“患者”包括哺乳动物。一方面，哺乳动物为人类。另一

方面，哺乳动物为非人类的灵长类动物，如猩猩以及其他猿和猴物种。一方面，哺乳动物为家养动物，如兔、狗或猫。另一方面，哺乳动物为农场动物，如牛、马、绵羊、山羊或猪。另一方面，哺乳动物为实验动物，包括啮齿类动物，如大鼠、小鼠和豚鼠等等。

[0019] 在此使用的“药学上可接受的盐”是指被公开化合物的衍生物，其母体化合物通过形成其酸或碱式盐而被修饰。药学上可接受的盐的例子包括，但不限于：碱性残基（如胺）的矿物盐或有机酸盐，酸性残基（如羧酸）的碱盐或有机盐等等。药学上可接受的盐包括（例如，由非毒性的无机酸或有机酸）形成的母体化合物的常规的非毒性盐或者季铵盐。例如，这样的常规的非毒性盐包括由无机酸得到的盐，如盐酸的、氢溴酸的、硫酸的、氨基磺酸的、磷酸的、硝酸的等等；以及由有机酸制备的盐，如乙酸的、丙酸的、琥珀酸的、羟乙酸的、硬脂酸的、乳酸的、苹果酸的、酒石酸的、柠檬酸的、抗坏血酸的、双羟萘酸的、马来酸的、羟基马来酸的、苯乙酸的、谷氨酸的、苯甲酸的、水杨酸的、对氨基苯磺酸的、2- 乙酰氧基苯甲酸的、反丁烯二酸的、甲苯磺酸的、甲磺酸的、乙烷二磺酸的、草酸的、羟乙磺酸的等等。

[0020] 在此使用的短语“药学上可接受的”与化合物、材料、组合物和 / 或剂型相关联使用，上述化合物、材料、组合物和 / 或剂型在健全的医疗判断范围内，适合用于在与合理的收益 / 风险比率相当的情况下，与人类或动物的组织接触而没有过度的毒性、刺激、过敏反应或其他问题或并发症。

[0021] 膀胱有两个重要的功能：储存尿和排空。储存尿发生在低压力下，这意味着在填充阶段逼尿肌松弛。膀胱的排空需要协调的逼尿肌的收缩和尿道括约肌的松弛。储存功能的紊乱可导致下泌尿道症状，如尿急、尿频和欲望性尿失禁，膀胱过度活动综合征的组成部分。膀胱过度活动综合征，这可能是由于在储存阶段膀胱平滑肌（逼尿肌）的非自主收缩，是一种常见和被低估的问题，在最近才评估其患病率。

[0022] 本申请的一方面涉及一种缓解尿频的方法。所述方法包括向需要其的受试者施用有效量的一种或多种镇痛剂和有效量的 α - 阻滞剂。在一些实施方式中，所述一种或多种镇痛剂和 α - 阻滞剂以不同剂型分别施用。在另外一些实施方式中，所述一种或多种镇痛剂和 α - 阻滞剂以单一剂型（例如以单一的丸剂或片剂）同时施用。在一些实施方式中，所述一种或多种镇痛剂和 α - 阻滞剂均被配制成施用后立即释放。在另外一些实施方式中，所述一种或多种镇痛剂和 α - 阻滞剂均被配制成施用后延迟释放。在另外一些实施方式中，所述一种或多种镇痛剂和 α - 阻滞剂均被配制成施用后延长释放。在另外一些实施方式中，所述一种或多种镇痛剂和 α - 阻滞剂均被配制成施用后延迟 - 延长释放。在另外一些实施方式中，所述一种或多种镇痛剂被配制成施用后延迟释放、延长释放或延迟 - 延长释放，而 α - 阻滞剂被配制成立即释放。在又一些实施方式中，所述一种或多种镇痛剂被制成立即释放，而 α - 阻滞剂被制成延迟释放、延长释放或延迟延长释放。所述方法能够被用于治疗夜尿症或活动过度的膀胱。本申请的另一方面涉及一种药物组合物，其包含：包括一种或多种镇痛剂的活性成分，α - 阻滞剂和药学上可接受的载体。

[0023] 阿尔法阻滞剂，也被称作 α - 肾上腺素能拮抗剂或 α - 阻滞剂，是一种担当 α - 肾上腺素能受体（其被进一步分为 α 1- 肾上腺素能受体和 α 2- 肾上腺素能受体）的受体拮抗剂的药物制剂。阿尔法阻滞剂可被分为选择性作用于 α 1- 肾上腺素能受体或 α 2- 肾上腺素能受体的选择性阻滞剂，以及作用于两种类型 α - 肾上腺素能受体的非选择性阿尔法阻滞剂。

[0024] 选择性 α1- 肾上腺素能阻滞剂的例子包括，但不限于 ：阿夫唑嗪、哌唑嗪、多沙唑嗪、坦洛新、特拉唑嗪、卡维地洛、柳胺苄心定和西洛多辛。选择性 α2- 肾上腺素能阻滞剂的例子包括，但不限于 ：阿替美唑、咪唑克生和育亨宾。非选择性 α- 肾上腺素能阻滞剂的例子包括 ：酚苄明、芬妥胺、苄唑啉、曲唑酮、典型及非典型抗精神病药物。

[0025] 在一些实施方式中，所述一种或多种镇痛剂以每日单独或联合剂量 50-2000mg，50-1500mg，50-1200mg，50-1000mg，50-800mg，50-600mg，50-500mg，50-400mg，50-300mg，50-250mg，50-200mg，50-100mg，100-2000mg，100-1500mg，100-1200mg，100-1000mg，100-800mg，100-600mg，100-500mg，100-400mg，100-300mg，100-200mg，200-2000mg，200-1500mg，200-1200mg，200-1000mg，200-800mg，200-600mg，200-400mg，400-2000mg，400-1500mg，400-1200mg，400-1000mg，400-800mg，400-600mg，600-2000mg，600-1500mg，600-1200mg，600-1000mg，600-800mg，800-2000mg，800-1500mg，800-1200mg，800-1000mg，1000-2000mg，1000-1500mg，1000-1200mg，1200-2000mg，1200-1500mg 或 1500-2000mg 口服施用 ；所述一种或多种 α- 阻滞剂以每日单独或联合剂量 0.01-100mg，0.01-30mg，0.01-10mg，0.01-3mg，0.01-1mg，0.01-0.3mg，0.01-0.1mg，0.01-0.03mg，0.03-100mg，0.03-30mg，0.03-10mg，0.03-3mg，0.03-1mg，0.03-0.3mg，0.03-0.1mg，0.1-100mg，0.1-30mg，0.1-10mg，0.1-3mg，0.1-1mg，0.1-0.3mg，0.3-100mg，0.3-30mg，0.3-10mg，0.3-3mg，0.3-1mg 和 0.2-1mg 口服施用。

[0026] 在一些实施方式中，所述 α- 阻滞剂为非选择性 α- 阻滞剂。在另外一些实施方式中，所述 α- 阻滞剂是选择性 α1- 肾上腺素能阻滞剂。在另外一些实施方式中，所述 α- 阻滞剂是选择性 α2- 肾上腺素能阻滞剂。在另外一些实施方式中，所述 α- 阻滞剂是坦洛新。

[0027] 本申请的另一方面涉及一种药物组合物，其包含 ：一种或多种镇痛剂 ；一种或多种 α- 阻滞剂 ；以及药学上可接受的载体。在一些实施方式中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚。

[0028] 在一些实施方式中，所述药物组合物包含单独或联合使用的用量为 50-2000mg，50-1500mg，50-1200mg，50-1000mg，50-800mg，50-600mg，50-500mg，50-400mg，50-300mg，50-250mg，50-200mg，50-100mg，100-2000mg，100-1500mg，100-1200mg，100-1000mg，100-800mg，100-600mg，100-500mg，100-400mg，100-300mg，100-200mg，200-2000mg，200-1500mg，200-1200mg，200-1000mg，200-800mg，200-600mg，200-400mg，400-2000mg，400-1500mg，400-1200mg，400-1000mg，400-800mg，400-600mg，600-2000mg，600-1500mg，600-1200mg，600-1000mg，600-800mg，800-2000mg，800-1500mg，800-1200mg，800-1000mg，1000-2000mg，1000-1500mg，1000-1200mg，1200-2000mg，1200-1500mg 或 1500-2000mg 的一种或多种镇痛剂 ；和用量为 0.01-100mg，0.01-30mg，0.01-10mg，0.01-3mg，0.01-1mg，0.01-0.3mg，0.01-0.1mg，0.01-0.03mg，0.03-100mg，0.03-30mg，0.03-10mg，0.03-3mg，0.03-1mg，0.03-0.3mg，0.03-0.1mg，0.1-100mg，0.1-30mg，0.1-10mg，0.1-3mg，0.1-1mg，0.1-0.3mg，0.3-100mg，0.3-30mg，0.3-10mg，0.3-3mg，0.3-1mg 和 0.2-1mg 的一种或多种 α- 阻滞剂。

[0029] 在一些实施方式中，所述 α- 阻滞剂为非选择性 α- 阻滞剂。在另外一些实施方式中，所述 α- 阻滞剂是选择性 α1- 肾上腺素能阻滞剂。在另外一些实施方式中，所述 α- 阻滞剂是选择性 α2- 肾上腺素能阻滞剂。在另外一些实施方式中，所述 α- 阻滞剂是坦洛新。

[0030] 在一些实施方式中，所述药物组合物包含量为 100-200mg，200-400mg，400-600mg，600-800mg，800-1000mg 或 1000-1200mg 的对乙酰氨基酚和量为 0.1-0.3mg，0.3-0.6mg，0.6

-0.9mg,0.9-1.2mg 或 1.2-1.5mg 的坦洛新。

[0031] 在另外一些实施方式中,所述一种或多种镇痛剂和一种或多种 α- 阻滞剂均被配制成立即释放。在另外一些实施方式中,所述一种或多种镇痛剂被配制成立即释放,而所述一种或多种 α- 阻滞剂被配制成延长释放。

[0032] 在另外一些实施方式中,所述一种或多种镇痛剂被配制成延长释放,而所述一种或多种 α- 阻滞剂被配制成立即释放。在一些实施方式中,所述一种或多种镇痛剂在一个时段或 5-24 小时、5-8 小时、8-16 小时或 16-24 小时内被连续地或者保持稳定速率地释放。在一些实施方式中,所述一种或多种镇痛剂的至少 90%在一个时段或 5-24 小时、5-8 小时、8-16 小时或 16-24 小时内被连续地或者保持稳定速率地释放。

[0033] 在另外一些实施方式中,所述一种或多种镇痛剂在施用 2 小时内被释放,而剩余部分在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或者保持稳定速率地释放。

[0034] 在另外一些实施方式中,所述一种或多种镇痛剂和所述一种或多种 α- 阻滞剂均被配制成延长释放。在一些实施方式中,所述一种或多种镇痛剂和所述一种或多种 α- 阻滞剂均被配制成延长释放,使得所述一种或多种镇痛剂和所述一种或多种 α- 阻滞剂在一个时段或 5-24 小时、5-8 小时、8-16 小时或 16-24 小时内被连续地或者保持稳定速率地释放。在另外一些实施方式中,所述一种或多种镇痛剂和所述一种或多种 α- 阻滞剂均被配制成具有两阶段释放曲线的延长释放,在该释放曲线中,所述一种或多种镇痛剂和所述一种或多种 α- 阻滞剂的 20-60%在施用 2 小时内被释放,而剩余部分在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或者保持稳定速率地释放。

[0035] 在一些实施方式中,所述药物组合物包含联合使用的用量为 50-1000mg,50-250mg,250-400mg,400-600mg,600-800mg 或 800-1000mg 的对乙酰氨基酚和用量为 0.1-1.2mg,0.1-0.3mg,0.3-0.6mg,0.6-0.9mg 或 0.9-1.2mg 的坦洛新,其中,该组合物被配制成对乙酰氨基酚和坦洛新均延长释放,其具有一种药物释放曲线,在该释放曲线中,对乙酰氨基酚和坦洛新的至少 90%在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或者保持稳定速率地释放。

[0036] 在另外一些实施方式中,所述药物组合物包含用量为 500-1000mg,50-200mg,50-400mg,100-400mg,100-300mg,200-400mg,400-600mg,600-800mg,800-1000mg 或 1000-1200mg 的对乙酰氨基酚和用量为 0.1-1.2mg,0.1-0.3mg,0.3-0.6mg,0.6-0.9mg 或 0.9-1.2mg 的坦洛新,其中,该组合物被配制成延长释放,其具有两阶段释放曲线,在该释放曲线中,对乙酰氨基酚和坦洛新的 20-60%在施用 2 小时内被释放,而剩余部分在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或者保持一个稳定速率地释放。

[0037] “延长释放”,又称持续释放(sustained-release,SR)、持续作用(sustained-action,SA)、限时释放(time-release,TR)、控制释(controlled-release,CR)、改良释放(modified release,MR)或缓释(continuous-release,CR),是一种在药物片剂或胶囊中使用以随着时间的过去缓慢溶解和释放活性成分的机制。延长释放的片剂或胶囊的优势在于,它们通常能够比同样药物的立即释放制剂更少频次的施用,而且,它们在血流中保持更稳定的药物水平,从而延长药物作用的持续时间并且降低药物在血流中的峰值量。例如,延长释放的镇痛剂能够使人整夜

安睡而不会起夜。

[0038] 在一个实施方式中，所述药物组合物通过在不溶物质（如丙烯酸酯类或甲壳质）的基质中包埋活性成分而被配制为延长释放的。延长释放形式被设计为通过在特定时段内维持恒定的药物水平而以预定的速率释放镇痛剂化合物。这可以通过不同的制剂实现，包括，但不限于，脂质体和药物－聚合物共轭体，如水凝胶。

[0039] 延长释放制剂能够被设计为以预定速率释放活性剂以维持特定的延长的时段内的恒定的药物水平，例如，在施用后或在与药物延迟释放相关的迟滞期后的最高至大约 24 小时、大约 20 小时、大约 16 小时、大约 12 小时、大约 10 小时、大约 9 小时、大约 8 小时、大约 7 小时、大约 6 小时、大约 5 小时、大约 4 小时、大约 3 小时、大约 2 小时或大约 1 小时。

[0040] 在某些优选的实施方式中，活性剂在大约 2 小时至大约 10 小时的时间间隔内释放。另外，活性剂也可以在大约 3 小时、大约 4 小时、大约 5 小时、大约 6 小时、大约 7 小时、大约 8 小时、大约 9 小时、大约 10 小时、大约 12 小时、大约 16 小时、大约 20 小时或大约 24 小时内释放。在另外一些实施方式中，活性剂在施用后大约 3 小时至大约 8 小时的时段内释放。

[0041] 在一些实施方式中，延长释放的制剂包括活性核，所述活性核由一种或多种惰性粒子组成，所述惰性粒子各自以其表面上包被有药物（例如，以含药物的包衣或成膜组合物的形式（使用例如流化床技术或本领域的技术人员公知的其他方法））的珠、丸剂、药丸、颗粒粒子、微胶囊、微球、微颗粒、纳米胶囊或纳米球的形式。所述惰性粒子可以是不同大小的，只要其足够大以保持不易溶解。或者，所述活性核可以通过含有药物成分的聚合物组合物的造粒和碾磨和／或通过挤出和滚圆来制备。

[0042] 所述活性剂可以通过本领域技术人员公知的技术被引入到惰性载体，例如，药物分层、粉末包衣、挤出／滚圆、滚压或造粒。在所述核中的药物的量将取决于所需要的剂量，且通常将为从约 5 至 90wt％变化。通常，基于包衣粒子的重量，根据所需的延滞时间和／或所选择的聚合物和包衣溶剂，在活性核上的聚合物包衣为约 1 至 50％。本领域的技术人员将能够选择在核上包被或引入核合适量的药物以实现所需的剂量。在一个实施方式中，无活性的核可以是糖球或缓冲晶体或封装缓冲晶体，如碳酸钙、碳酸氢钠、富马酸、酒石酸等，它们改变药物的微环境以促进其释放。

[0043] 本申请的另一方面涉及一种缓解尿频的方法。所述方法包括向需要其的受试者施用一种或多种有效量的镇痛剂，和有效量的 5α－还原酶抑制剂。5α－还原酶抑制剂的例子包含，但不限于：非那雄胺、贝氯特来、爱普列特、艾宗特来、拉匹雄胺（lapisteride）和妥罗雄脲。在一些实施方式中，5α－还原酶抑制剂为非那雄胺。

[0044] 在一些实施方式中，所述一种或多种镇痛剂和 5α－还原酶抑制剂以不同剂型分别施用。在另外一些实施方式中，所述一种或多种镇痛剂和 α－阻滞剂以单一剂型（例如以单一丸剂或片剂）同时施用。在一些实施方式中，所述一种或多种镇痛剂和 5α－还原酶抑制剂均被配制成施用后立即释放。在另外一些实施方式中，所述一种或多种镇痛剂和 5α－还原酶抑制剂均被配制成施用后延迟释放。在另外一些实施方式中，所述一种或多种镇痛剂和 5α－还原酶抑制剂均被配制成施用后延长释放。在另外一些实施方式中，所述一种或多种镇痛剂和 5α－还原酶抑制剂均被配制成施用后延迟－延长释放。在另外一些实施方式中，所述一种或多种镇痛剂被配制成延迟释放、延长释放或延迟延长释放，而 5α－还

原酶抑制剂被配制成立即释放。在又一些实施方式中，所述一种或多种镇痛剂被配制成立即释放，而 5α－还原酶抑制剂被配制成延迟释放、延长释放或延迟－延长释放。所述方法能够被用于治疗夜尿症或活动过度的膀胱。本申请的另一方面涉及一种药物组合物，其包含：包括一种或多种镇痛剂的活性成分，5α－还原酶抑制剂和药学上可接受的载体。

[0045] 在一些实施方式中，所述一种或多种镇痛剂以每日单独或联合剂量 50-2000mg，50-1500mg，50-1200mg，50-1000mg，50-800mg，50-600mg，50-500mg，50-400mg，50-300mg，50-250mg，50-200mg，50-100mg，100-2000mg，100-1500mg，100-1200mg，100-1000mg，100-800mg，100-600mg，100-500mg，100-400mg，100-300mg，100-200mg，200-2000mg，200-1500mg，200-1200mg，200-1000mg，200-800mg，200-600mg，200-400mg，400-2000mg，400-1500mg，400-1200mg，400-1000mg，400-800mg，400-600mg，600-2000mg，600-1500mg，600-1200mg，600-1000mg，600-800mg，800-2000mg，800-1500mg，800-1200mg，800-1000mg，1000-2000mg，1000-1500mg，1000-1200mg，1200-2000mg，1200-1500mg 或 1500-2000mg 口服施用；而 5α－还原酶抑制剂以每日单独或联合剂量 0.1-250mg，0.1-100mg，0.1-30mg，0.1-10mg，0.1-3mg，0.1-1mg，0.3-250mg，0.3-100mg，0.3-30mg，0.3-10mg，0.3-3mg，0.3-1mg，1-100mg，1-30mg，1-10mg，1-3mg，3-7mg 和 4-6mg 口服施用。

[0046] 在一些实施方式中，该 5α－还原酶抑制剂为坦洛新。

[0047] 本申请的另一方面涉及一种药物组合物，其包含：一种或多种镇痛剂、一种或多种 5α－还原酶抑制剂；和药学上可接受的载体。在一些实施方式中，所述一种或多种镇痛剂选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚。

[0048] 在一些实施方式中，所述药物组合物包含单一或联合的用量为 50-2000mg，50-1500mg，50-1200mg，50-1000mg，50-800mg，50-600mg，50-500mg，50-400mg，50-300mg，50-250mg，50-200mg，50-100mg，100-2000mg，100-1500mg，100-1200mg，100-1000mg，100-800mg，100-600mg，100-500mg，100-400mg，100-300mg，100-200mg，200-2000mg，200-1500mg，200-1200mg，200-1000mg，200-800mg，200-600mg，200-400mg，400-2000mg，400-1500mg，400-1200mg，400-1000mg，400-800mg，400-600mg，600-2000mg，600-1500mg，600-1200mg，600-1000mg，600-800mg，800-2000mg，800-1500mg，800-1200mg，800-1000mg，1000-2000mg，1000-1500mg，1000-1200mg，1200-2000mg，1200-1500mg 或 1500-2000mg 的一种或多种镇痛剂；和用量为 0.1-250mg，0.1-100mg，0.1-30mg，0.1-10mg，0.1-3mg，0.1-1mg，0.3-250mg，0.3-100mg，0.3-30mg，0.3-10mg，0.3-3mg，0.3-1mg，1-100mg，1-30mg，1-10mg，1-3mg，3-7mg 和 4-6mg 的一种或多种 5α－还原酶抑制剂。

[0049] 在一些实施方式中，α－阻滞剂是非选择性 α－阻滞剂。在另外一些实施方式中，α－阻滞剂是选择性 α1-肾上腺素能阻滞剂。在另外一些实施方式中，α－阻滞剂是选择性 α2-肾上腺素能阻滞剂。在另外一些实施方式中，α－阻滞剂是坦洛新。

[0050] 在一些实施方式中，所述药物组合物包含用量为 100-200mg，200-400mg，400-600mg，600-800mg，800-1000mg 或 1000-1200mg 的对乙酰氨基酚和用量为 0.1-0.3mg，0.3-0.6mg，0.6-0.9mg，0.9-1.2mg 或 1.2-1.5mg 的非那雄胺。

[0051] 在另外一些实施方式中，所述一种或多种镇痛剂和所述一种或多种 5α－还原酶抑制剂均被配制成立即释放。在另外一些实施方式中，所述一种或多种镇痛剂被配制成立即释放，而所述一种或多种 α－阻滞剂被配制成延长释放。

[0052] 在另外一些实施方式中，所述一种或多种镇痛剂被配制成延长释放，而所述一种或多种 5α－还原酶抑制剂被配制成立即释放。在一些实施方式中，所述一种或多种镇痛剂在一个时段或 5-24 小时、5-8 小时、8-16 小时或 16-24 小时内被连续地或以稳定速率释放。在一些实施方式中，所述一种或多种镇痛剂的至少 90％在一个时段或 5-24 小时、5-8 小时、8-16 小时或 16-24 小时内被连续地或以稳定速率释放。

[0053] 在另外的一些实施方式中，所述一种或多种镇痛剂在施用 2 小时内释放，而剩余部分在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或以稳定速率释放。

[0054] 在另外一些实施方式中，所述一种或多种镇痛剂和所述一种或多种 5α－还原酶抑制剂均被配制成延长释放。在一些实施方式中，所述一种或多种镇痛剂和所述一种或多种 5α－还原酶抑制剂均被配制成延长释放，使得所述一种或多种镇痛剂和所述一种或多种 5α－还原酶抑制剂在一个时段或 5-24 小时、5-8 小时、8-16 小时或 16-24 小时内被连续地或以稳定速率释放。在另外的一些实施方式中，所述一种或多种镇痛剂和所述一种或多种 5α－还原酶抑制剂均被配制成具有两阶段释放曲线的延长释放，在该两阶段释放曲线中，所述一种或多种镇痛剂和所述一种或多种 5α－还原酶抑制剂的 20-60％在施用 2 小时内释放，而剩余部分在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或以稳定速率释放。

[0055] 在一些实施方式中，所述药物组合物包含用量为 50-1000mg，50-250mg，250-400mg，400-600mg，600-800mg 或 800-1000mg 的对乙酰氨基酚和联合使用的用量为 1-20mg，1-3mg，3-7mg，7-10mg，10-15mg 或 15-20mg 的非那雄胺，其中，该组合物中的对乙酰氨基酚和非那雄胺均被配制成具有一种药物释放曲线的延长释放，在该药物释放曲线中，对乙酰氨基酚和非那雄胺的至少 90％在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或以稳定速率释放。

[0056] 在另外一些实施方式中，所述药物组合物包含用量为 50-1000mg，50-100mg，50-200mg，50-300mg，50-400mg，50-600mg，50-800mg，100-200mg，100-300mg，100-400mg，100-600mg，100-800mg，100-1000mg，200-400mg，200-600mg，200-800mg，200-1000mg，400-600mg，400-800mg，400-1000mg，600-800mg，600-1000mg，800-1000mg 或 1000-1200mg 的对乙酰氨基酚和用量为 1-20mg，1-3mg，1-7mg，1-10mg，1-15mg，3-7mg，3-10mg，3-15mg，3-20mg，7-10mg，7-15mg，7-20mg，10-15mg，10-20mg 或 15-20mg 的非那雄胺，其中，该组合物被配制成具有两阶段释放曲线的延长释放，在该两阶段释放曲线中，对乙酰氨基酚和非那雄胺的 20-60％在施用 2 小时内释放，而剩余部分在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或以稳定速率释放。

[0057] “延长释放”，又称持续释放 (sustained-release，SR)、持续作用 (sustained-action，SA)、限时释放 (time-release，TR)、控制释放 (controlled-release，CR)、改良释放 (modified release，MR) 或缓释 (continuous-release，CR)，是一种在药物片剂或胶囊中使用以随着时间的过去缓慢溶解和释放活性成分的机制。延长释放的片剂或胶囊的优势在于，它们通常能够比同样药物的立即释放制剂更少频次的施用，而且，它们在血流中保持更稳定的药物水平，从而延长药物作用的持续时间和降低药物在血流中的峰值量。例如，延长释放的镇痛剂能够使人整夜安睡而不会起夜。

[0058] 在一个实施方式中，所述药物组合物通过在不溶物质（如丙烯酸酯类或甲壳质）的基质中包埋活性成分而被配制为延长释放的。延长释放形式被设计为通过在一段特定的时段内维持恒定的药物水平而以预定的速率释放镇痛剂化合物。这可以通过不同的制剂实现，包括，但不限于，脂质体和药物－聚合物共轭共轭体，如水凝胶。

[0059] 延长释放的制剂可被设计为以预定速率释放活性成分以维持特定的延长的时段的恒定的药物水平，例如，在施用后，或者在与药物延迟释放相关的迟滞期后最高至约 24 小时、约 20 小时、约 16 小时、约 12 小时、约 10 小时、约 9 小时、约 8 小时、约 7 小时、约 6 小时、约 5 小时、约 4 小时、约 3 小时、约 2 小时或约 1 小时。

[0060] 在某些优选的实施方式中，活性剂在约 2 小时至约 10 小时之间的时间间隔期间释放。或者，活性剂在约 3 小时、约 4 小时、约 5 小时、约 6 小时、约 7 小时、约 8 小时、约 9 小时、约 10 小时、约 12 小时、约 16 小时、约 20 小时或约 24 小时内释放。在其他一些实施方式中，活性剂在施用后约三小时至约八小时之间的时段内释放。

[0061] 在一些实施方式中，延长释放制剂包括活性核，所述活性核由一种或多种惰性粒子组成，所述惰性粒子各自以其表面上包被有药物（例如，以含药物的包衣或成膜组合物的形式（使用例如流化床技术或本领域的技术人员公知的其他方法））的珠、丸剂、药丸、颗粒粒子、微胶囊、微球、微颗粒、纳米胶囊或纳米球的形式。所述惰性粒子可以是不同大小的，只要其足够大以保持不易溶解。或者，所述活性核可以通过含有药物成分的聚合物组合物的造粒和碾磨和／或通过挤出和滚圆来制备。

[0062] 所述活性剂可以通过本领域技术人员公知的技术被引入到惰性载体，例如，药物分层、粉末包衣、挤出／滚圆、滚压或造粒。在所述核中的药物的量将取决于所需要的剂量，且通常将为从约 5 至 90wt％变化。通常，基于包衣粒子的重量，根据所需的延滞时间和／或所选择的聚合物和包衣溶剂，在活性核上的聚合物包衣为约 1 至 50％。本领域的技术人员将能够选择在核上包被或引入核合适量的药物以实现所需的剂量。在一个实施方式中，无活性的核可以是糖球或缓冲晶体或封装缓冲晶体，如碳酸钙、碳酸氢钠、富马酸、酒石酸等，它们改变药物的微环境以促进其释放。

[0063] 所述延长释放的制剂可使用各种延长释放包衣或有助于活性剂随时间逐渐释放的机制。在一些实施方式中，延长释放的制剂包含通过控制溶解释放而控制释放的聚合物。在特别的实施方式中，活性剂被并入含有不溶的聚合物和由不同厚度的聚合物材料包覆的药物粒子或颗粒的基质中。聚合物材料可包括含有蜡状材料的类脂屏障，如巴西棕榈蜡、蜂蜡、鲸蜡、小烛树蜡、紫胶蜡 (shellac wax)、可可豆脂、十六十八醇 (cetostearyl alcohol)、部分氢化的植物油、地蜡、石蜡、地蜡、肉豆蔻醇、硬脂醇、鲸蜡醇和硬脂酸，连同表面活性剂，如聚氧乙烯失水山梨醇单油酸酯 (polyoxyethylenesorbitan monooleate)。当与水性介质（如生物体液）接触时，根据聚合物包衣的厚度，在预定的滞后时间以后，聚合物包衣被乳化或侵蚀。所述滞后时间与胃肠蠕动、pH 值或在胃内的滞留时间 (gastric residence) 无关。

[0064] 在其他实施方式中，延长释放的制剂包含实现控制扩散释放的聚合物基质。所述基质可包含一种或多种亲水的和／或水溶胀性的形成基质的聚合物，依赖于 pH 值的聚合物和／或不依赖于 pH 值的聚合物。

[0065] 在一个实施方式中，所述延长释放的制剂包含水溶性的或水溶胀性的形成基质的

聚合物，非必须地包含一种或多种增溶辅料和 / 或促进释放剂。随着水溶性聚合物的增溶作用，活性剂溶解（如果可溶），且通过基质的含水部分逐渐扩散。由于更多的水渗入到基质核心中，凝胶层随时间生长，增加了凝胶层的厚度并提供了药物释放的扩散屏障。随着外层变得完全水化，聚合物链完全舒展，且不能再保持凝胶层的完整性，导致在基质的表面上的外层水化的聚合物解开缠结和侵蚀。水继续通过凝胶层向核心渗入，直到其完全被侵蚀。可溶的药物通过这种扩散和侵蚀的联合作用释放，而对于不溶性药物，不论剂量如何，侵蚀都是主要机制。

[0066] 与此相似的，水溶胀性聚合物通常在生物体液中水化并溶胀，形成匀质的基质结构，该结构在药物释放期间保持其形状，并作为用于药物的载体、增溶剂和 / 或释放促进剂。初始的基质聚合物水合阶段导致药物缓慢释放（迟滞阶段）。一旦水溶胀性聚合物完全水合并溶胀，基质中的水可以同样地溶解药物物质，并使其通过基质包衣扩散出来。

[0067] 此外，由于依赖 pH 值的释放促进剂的浸出，基质的孔隙率能够增加，从而以更快的速率释放药物。随后，药物释放速率变为恒定，且其成为通过水合的聚合物凝胶的药物扩散的函数。从基质的释放速率依赖于不同的参数，包括聚合物类型和等级 ；药物溶解性和剂量 ；聚合物与药物的比例 ；填料类型和等级 ；聚合物与填料的比例 ；药物和聚合物的粒径 ；以及基质的孔隙率和形状。

[0068] 示例性的亲水性和 / 或水溶胀性形成基质的聚合物包括，但不限于，纤维素聚合物，包括羟烷基纤维素和羧烷基纤维素，如羟丙基甲基纤维素 (HPMC)、羟丙基纤维素 (HPC)、羟乙基纤维素 (HEC)、甲基纤维素 (MC)、羧甲基纤维素 (CMC)，粉状纤维素，如微晶纤维素、乙酸纤维素、乙基纤维素、其盐、及其组合物 ；藻酸盐、树胶，包括杂多糖胶以及同多糖胶，如黄原胶、黄芪胶、果胶、阿拉伯胶、梧桐胶、藻酸盐、琼脂、瓜尔胶、羟丙基瓜尔胶、硅酸镁铝、角叉藻聚糖、豆角胶、胶凝糖胶、及其衍生物 ；丙烯酸系树脂，包括丙烯酸、甲基丙烯酸、丙烯酸甲酯和甲基丙烯酸甲酯的聚合物和共聚物，以及交联的聚丙烯酸衍生物，如卡波姆（例如，Carbopol®，如，包括 Carbopol® 71G NF，具有不同分子量等级，来自 Noveon 公司，俄亥俄州辛辛那提市）；鹿角菜胶 ；聚乙酸乙烯酯（例如，KOLLIDON® SR）；聚乙烯吡咯烷酮及其衍生物，如交聚维酮 ；聚氧化乙烯 ；以及聚乙烯醇。优选的亲水性和水溶胀性聚合物包括纤维素聚合物，特别是 HPMC。

[0069] 所述延长释放的制剂可进一步包含至少一种粘合剂，该粘合剂能够使亲水性化合物交联以在水性介质（包括生物体液）中形成亲水性聚合物基质（即，凝胶基质）。

[0070] 示例性的粘合剂包括同多糖，如半乳甘露聚糖胶、瓜尔胶、羟丙基瓜尔胶、羟丙基纤维素 (HPC ；如 Klucel EXF) 以及豆角胶。在其他实施方式中，所述粘合剂为海藻酸衍生物、HPC 或微晶纤维素 (MCC)。其他的粘合剂包括，但不限于，淀粉、微晶纤维素、羟丙基纤维素、羟乙基纤维素、羟丙基甲基纤维素和聚乙烯吡咯烷酮。

[0071] 在一个实施方式中，引入方法为通过向惰性载体上喷射活性剂和粘合剂的悬浮液的药物分层。

[0072] 所述粘合剂可以在珠型制剂中以约 0.1wt％至约 15wt％，且优选约 0.2wt％至约 10wt％的含量存在。

[0073] 在一些实施方式中，所述亲水性聚合物基质可进一步包含离子聚合物、非离子聚

合物或不溶于水的疏水性聚合物，以提供更强大的凝胶层和 / 或减少基质中孔隙的数量和尺寸，从而减慢扩散和侵蚀速度以及伴随的活性剂的释放。这可以额外抑制最初爆发效果，并产生更稳定的活性剂的“零级释放”。

[0074] 示例性的用于减慢溶出速率的离子聚合物包括阴离子聚合物和阳离子聚合物。示例性的阴离子聚合物包括，例如，羧甲基纤维素钠 (Na CMC)、海藻酸钠、丙烯酸或卡波姆的聚合物（如CARBOPOL® 934、940、974P NF）；肠溶聚合物 (enteric polymer)，如聚醋酸乙烯邻苯二甲酸酯 (PVAP)、甲基丙烯酸共聚物（如EUDRAGIT® L100、L 30D 55、A 和 FS 30D）、羟丙基甲基纤维素乙酸琥珀酸酯 (AQUAT HPMCAS)；以及黄原胶。示例性的阳离子聚合物包括，例如，甲基丙烯酸二甲氨基乙酯共聚物（例如，EUDRAGIT® E 100）。与仅有亲水性聚合物相比，阴离子聚合物，尤其是肠溶聚合物的引入对于形成针对弱碱性的药物的不依赖于 pH 值的释放曲线是有用的。

[0075] 示例性的用于减慢溶出速率的非离子聚合物包括，例如，羟丙基纤维素 (HPC) 和聚氧化乙烯 (PEO)（例如，POLYOX™）。

[0076] 示例性的疏水性聚合物包括乙基纤维素（例如，ETHOCEL™, SURELEASE®）、乙酸纤维素、甲基丙烯酸共聚物（例如，EUDRAGIT® NE30D）、季胺基甲基丙烯酸酯共聚物（如，EUDRAGIT® RL 100 或 PO RS100）、聚乙酸乙烯酯、甘油单硬脂酸酯、脂肪酸，如柠檬酸乙酰基三丁酯，及其组合和衍生物。

[0077] 所述溶胀性聚合物可以以 1wt％至 50wt％，优选 5wt％至 40wt％，最优选 5wt％至 20wt％的比例并入制剂中。所述溶胀性聚合物和粘合剂可以在造粒前或者造粒后并入制剂中。所述聚合物也可以分散在有机溶剂或水性醇中并在造粒期间被喷射。

[0078] 示例性的促进释放剂包括依赖于 pH 值的肠溶聚合物，所述依赖于 pH 值的肠溶聚合物在 pH 值低于约 4.0 时保持完整，且在 pH 值高于 4.0，优选高于 5.0，最优选高于 6.0 时溶解，且认为其在本发明中作为促进释放剂是有用的。示例性的依赖 pH 值的聚合物包括，但不限于，甲基丙烯酸共聚物、甲基丙烯酸 - 甲基丙烯酸甲酯共聚物（如德国 Rohm 股份有限公司的 EUDRAGIT® L100(A 型）、EUDRAGIT® S100(B 型））；甲基丙烯酸 - 丙烯酸乙酯共聚物（如德国 Rohm 股份有限公司的 EUDRAGIT® L100-55(C 型）和 EUDRAGIT® L30D-55 共聚物分散）；甲基丙烯酸 - 甲基丙烯酸甲酯和甲基丙烯酸甲酯的共聚物（EUDRAGIT® FS）；甲基丙烯酸、甲基丙烯酸酯和丙烯酸乙酯的三元共聚物；醋酸邻苯二甲酸纤维素 (CAP)；羟丙基甲基纤维素邻苯二甲酸酯 (HPMCP)（例如，日本信越化学的 HP-55、HP-50、HP-55S）；聚醋酸乙烯邻苯二甲酸酯 (PVAP)（例如，COATERIC®， OPADRY®肠道白 (enteric white)OY-P-7171）；聚乙酸丁酸乙烯酯；醋酸纤维素琥珀酸酯 (CAS)；羟丙基甲基纤维素醋酸酯琥珀酸酯 (HPMCAS)，例如，HPMCAS LF 级、MF 级、HF 级，包括 AQOAT® LF 和 AQOAT® MF（日本信越化学）；日本信越化学）；虫胶（例如，MARCOAT™ 125 和 MARCOATTM 125N）；乙酸乙烯酯 - 马来酸酐共聚物；

苯乙烯 - 马来单酯共聚物 (styrene-maleic monoester copolymer) ;羧甲基乙基纤维素 (CMEC, Freund 公司, 日本) ;醋酸邻苯二甲酸纤维素 (CAP)(例如, AQUATERIC®) ;乙酸 -1,2,4- 苯三酸纤维素 (CAT) ;以及重量比在约 2 ： 1 至约 5 ： 1 的其两种或更多种混合物, 例如, 如重量比为约 3 ： 1 至约 2 ： 1 的 EUDRAGIT® L 100-55 和 EUDRAGIT® S 100 的混合物, 或重量比为约 3 ： 1 至约 5 ： 1 的 EUDRAGIT® L 30D-55 和 EUDRAGIT® FS 的混合物。

[0079] 这些聚合物可以单独使用或者组合使用, 或者与上述以外的聚合物一起使用。优选的依赖 pH 值的肠溶聚合物为药学上可接受的甲基丙烯酸共聚物。这些共聚物为基于甲基丙烯酸和甲基丙烯酸甲酯的阴离子聚合物, 且其优选具有约 135,000 的平均分子量。在这些共聚物中, 自由羧基与甲酯化的羧基的比例的范围为, 例如, 1 ： 1 至 1 ： 3, 例如, 大约 1 ： 1 或 1 ： 2。此聚合物在商业上以 Eudragit® 商标名有售, 如 Eudragit L 系列, 例如, Eudragit L 12.5®、Eudragit L 12.5P®、Eudragit L 100®、Eudragit L 100-55®、Eudragit L-30D®、Eudragit L-30 D-55®, Eudragit S® 系列, 例如, Eudragit S 12.5®、Eudragit S 12.5P®、Eudragit S100®。释放促进剂并不限于依赖于 pH 值的聚合物。其他迅速溶解且迅速使剂型浸出而留下多孔结构的亲水性分子也可用于相同的目的。

[0080] 促进释放剂可以以剂型单元的 10wt％至 90wt％、优选 20wt％至 80wt％、且最优选 30wt％至 70wt％的量并入。所述试剂可以在造粒前或者造粒后并入制剂中。所述促进释放剂可以作为干燥材料加入到制剂中, 或者其可以分散或溶解到合适的溶剂中, 并在造粒期间分散。

[0081] 在一些实施方式中, 所述基质可包括释放促进剂和增溶剂的组合。所述增溶剂可以是离子型或非离子型表面活性剂、络合剂、亲水性聚合物、pH 值调节剂 (如酸化剂和碱化剂)、以及通过分子包埋增加难溶性药物的溶解度的分子。几种增溶剂可以同时使用。

[0082] 增溶剂可包括表面活性剂, 如多库酯钠、硫酸月桂酯钠、硬脂酰醇富马酸钠、吐温类 (Tweens®) 和司盘类 (Spans)(PEO 改性的山梨醇单酯和脂肪酸山梨醇酯)、聚 (环氧乙烷)- 聚环氧丙烷 - 聚 (环氧乙烷) 嵌段共聚物 (又名 PLURONICS™) ;络合剂, 如低分子量聚乙烯吡咯烷酮和低分子量羟丙基甲基纤维素 ;通过分子包埋而有助于溶解度的分子, 如环糊精 ;以及 pH 值调节剂, 包括酸化剂, 如柠檬酸、富马酸、酒石酸和盐酸 ;以及碱化剂, 如葡甲胺和氢氧化钠。

[0083] 增溶剂通常构成剂型的 1wt％至 80wt％, 优选 1wt％至 60wt％, 更优选 1wt％至 50wt％, 且其可以以不同的方式并入。它们可以在造粒前以干燥或湿润的方式并入制剂中。它们也可以在其他材料造粒或者其他工艺以后加入制剂中。在造粒期间, 增溶剂可以以溶液形式添加或者不添加粘合剂喷射。

[0084] 在一些实施方式中, 所述延长释放的制剂包含聚合物基质, 其能够不依赖 pH 值在一定时间以后释放药物。对于本发明的目的而言, “不依赖 pH 值”被定义为具有本质上不受 pH 值影响的特性 (例如, 溶解)。不依赖 pH 值的聚合物通常是指“时间控制”或“依赖于时

间”的释放曲线的情况。

[0085] 不依赖于 pH 值的聚合物可以用于包覆活性剂和 / 或提供用于在其上的延长释放包衣中的亲水性基质的聚合物。不依赖 pH 值的聚合物可以是不溶于水或溶于水的。不溶于水的不依赖 pH 值的聚合物的例子包括，但不限于，具有小部分氯化三甲铵乙基甲基丙烯酸酯的中性的甲基丙烯酸酯（例如，EUDRAGIT® RS 和 EUDRAGIT® RL ；无任何官能团的中性酯分散体，（例如，EUDRAGIT® NE30D 和 EUDRAGIT® NE30）；纤维素聚合物，如乙基纤维素、羟乙基纤维素、醋酸纤维素或混合物；以及其他不依赖 pH 值的包衣产品。示例性的水溶性的不依赖 pH 值的聚合物包括羟烷基纤维素醚，如羟丙基甲基纤维素 (HPMC) 和羟丙基纤维素 (HPC)；聚乙烯吡咯烷酮 (PVP)、甲基纤维素、OPADRY® amb、瓜尔胶、黄原胶、阿拉伯胶、羟乙基纤维素，以及丙烯酸乙酯和甲基丙烯酸甲酯共聚物分散体，或其组合。

[0086] 在一个实施方式中，所述延长释放的制剂包含不溶于水的透水聚合物包衣或者基质，其包括形成在活性核上的一种或多种不溶于水的透水膜。所述包衣可额外包含一种或多种水溶性的聚合物和 / 或一种或多种增塑剂。不溶于水的聚合物包衣包括用于释放核中的活性剂的隔离包衣，其中，与较高粘度等级相比，较低分子量（粘度）等级显示出更快的释放速率。

[0087] 在优选的实施方式中，不溶于水的成膜聚合物包括一种或多种烷基纤维素醚，如乙基纤维素及其混合物，（例如，等级为 PR100、PR45、PR20、PR10 和 PR7 的乙基纤维素；ETHOCEL®，Dow 公司）。

[0088] 示例性的水溶性聚合物，如聚乙烯吡咯烷酮（POVIDONE®）、羟丙基甲基纤维素、羟丙基纤维素及其混合物。

[0089] 在一些实施方式中，不溶于水的聚合物在不需要增塑剂的情况下提供了合适的性能（例如，延长释放特性、机械性能和包覆性能）。例如，可以使用含有如下物质的包衣而无需增塑剂：聚乙酸乙烯酯 (PVA)、丙烯酸酯 / 甲基丙烯酸酯的中性共聚物（如，由 Evonik Industries 的商业可用的 Eudragit NE30D)、乙基纤维素与羟丙基纤维素共同应用、蜡等。

[0090] 在又一个实施方式中，不溶于水的聚合物基质可进一步包含增塑剂。所需的增塑剂的含量取决于增塑剂、不溶于水的聚合物的性能以及最终所需的包衣的性能。相对于包衣的总重量，增塑剂的合适的水平为约 1wt％至约 20wt％、约 3wt％至约 20wt％、约 3wt％至约 5wt％、约 7wt％至约 10wt％、约 12wt％至约 15wt％、约 17wt％至约 20wt％、或约 1wt％、约 2wt％、约 3wt％、约 4wt％、约 5wt％、约 6wt％、约 7wt％、约 8wt％、约 9wt％、约 10wt％、约 15wt％或约 20wt％，包括其中的所有范围和子范围。

[0091] 示例性的增塑剂包括，但不限于，三乙酸甘油酯、乙酰单酸甘油乙酯，油（蓖麻油、氢化蓖麻油、菜籽油、芝麻油、橄榄油等）；柠檬酸酯、柠檬酸三乙酯、柠檬酸乙酰基三乙酯、柠檬酸乙酰基三丁酯、柠檬酸三丁酯、柠檬酸乙酰基三正丁酯、邻苯二甲酸二乙酯、邻苯二甲酸二丁酯、邻苯二甲酸二辛酯、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、对羟基苯甲酸丙酯、对羟基苯甲酸丁酯、癸二酸二乙酯、癸二酸二丁酯、甘油三丁酸酯、取代甘油三酯和甘油脂、单乙酰化和双乙酰化甘油脂（如 MYVACET® 9-45）、单硬脂酸甘油酯、甘油三丁酸

酯、聚山梨醇酯 80、聚乙二醇（如 PEG-4000、PEG-400）、丙二醇、1,2- 丙二醇、甘油、山梨醇、草酸二乙酯、苹果酸二乙酯、富马酸二乙酯、二乙基丙二酸酯、丁二酸二丁酯、脂肪酸、甘油、山梨醇、草酸二乙酯、二乙基苹果酸酯、马来酸二乙酯、延胡索酸二乙酯、琥珀酸二乙酯、丙二酸二乙酯、邻苯二甲酸二辛酯、癸二酸二丁酯及其混合物。所述增塑剂可以具有表面活性剂的性质，从而其可以作为释放调节剂。例如，可以使用非离子型洗涤剂，如 Brij 58（聚氧乙烯 (20) 十六烷基醚）等。

[0092] 增塑剂可以是用于赋予其他的硬或脆的聚合物材料弹性的高沸点的有机溶剂，且其能影响活性剂的释放曲线。增塑剂通常会引起沿聚合物链的内聚的分子间力的减少，从而导致多种聚合物性能的变化，包括聚合物的抗拉强度的降低、伸长率的增加以及玻璃化转变温度或软化温度的下降。例如，增塑剂的含量和选择可以影响片剂的硬度，甚至可以影响其溶解或崩解性能，以及其物理和化学稳定性。一些增塑剂可以增加包衣的弹性和 / 或可挠性，从而降低包衣的脆性。

[0093] 在另一个实施方式中，所述延长释放的制剂包含至少两种形成凝胶的聚合物的组合，其包括至少一种非离子型形成凝胶的聚合物和 / 或至少一种阴离子型形成凝胶的聚合物。由形成凝胶的聚合物的组合形成的凝胶提供了控制释放，使得当制剂被摄入并接触到胃肠液时，最接近表面的聚合物水合以形成粘性凝胶层。由于高粘度，粘性层仅能逐渐溶解掉，以相同的过程露出下面的材料。因此，物质缓慢溶解掉，从而慢慢将活性成分释放到胃肠液。至少两种形成凝胶的聚合物的组合使得产生的凝胶的性能（如粘性）能够被操纵以提供所需的释放曲线。

[0094] 在一个特定的实施方式中，所述制剂包含至少一种非离子型形成凝胶的聚合物和至少一种阴离子型形成凝胶的聚合物。在另一个实施方式中，所述制剂包含两种不同的非离子型形成凝胶的聚合物。在又一个实施方式中，所述制剂包含相同化学性质但具有不同的溶解度、粘度和 / 或分子量的非离子型的形成凝胶的聚合物的组合（例如不同粘度等级的羟丙基甲基纤维素的组合，如 HPMC K100 和 HPMC K15M 或 HPMC K100M）。

[0095] 示例性的阴离子型形成凝胶的聚合物包括，但不限于，羧甲基纤维素钠 (NaCMC)；羧甲基纤维素 (CMC)；阴离子型多糖，如海藻酸钠、海藻酸、果胶、聚葡糖醛酸（聚 α- 和 -β-1,4- 葡萄糖醛酸）、聚半乳糖醛酸（果胶酸）、硫酸软骨素、角叉藻聚糖、帚叉藻聚糖 (furcellaran)；阴离子胶，如黄原胶；丙烯酸或卡波姆的聚合物（如 Carbopol® 934、940、974P NF）；Carbopol® 共聚物；Pemulen® 聚合物；聚卡波非等。

[0096] 示例性的非离子型的形成凝胶的聚合物包括，但不限于，聚维酮 (PVP，聚乙烯吡咯烷酮）、聚乙烯醇、PVP 和聚乙酸乙烯酯的共聚物、HPC（羟丙基纤维素）、HPMC（羟丙基甲基纤维素）、羟乙基纤维素、羟甲基纤维素、明胶、聚环氧乙烷、阿拉伯树胶、糊精、淀粉、聚甲基丙烯酸羟乙酯 (PHEMA)、水溶性非离子型聚甲基丙烯酸酯及其共聚物、改性纤维素、改性多糖、非离子型胶、非离子型多糖和 / 或其混合物。

[0097] 所述制剂可非必须地包含上述的肠溶聚合物，和 / 或至少一种赋形剂，如填料、粘合剂（如上所述）、崩解剂、和 / 或流动性助剂或助流剂。

[0098] 示例性的填料包括但不限于，乳糖、葡萄糖、果糖、蔗糖、磷酸二钙、糖醇，也称“糖多醇”，如山梨醇、甘露醇 (manitol)、拉克替醇、木糖醇、异麦芽酮糖醇 (isomalt)、赤藓糖醇

和氢化淀粉水解物（多种糖醇的混合物）、玉米淀粉、马铃薯淀粉、羧甲基纤维素钠、乙基纤维素、乙酸纤维素、肠溶聚合物，或其混合物。

[0099] 示例性的粘合剂包括但不限于，水溶性亲水性聚合物，如聚维酮（PVP，聚乙烯吡咯烷酮），共聚维酮（聚乙烯吡咯烷酮和聚乙酸乙烯酯的共聚物），低分子量的 HPC（羟丙基纤维素），低分子量的 HPMC（羟丙基甲基纤维素），低分子量的羧甲基纤维素，乙基纤维素，明胶，聚环氧乙烷，阿拉伯树胶，糊精，硅酸镁铝，淀粉和聚甲基丙烯酸酯类，如 Eudragit NE 30D、Eudragit RL、Eudragit RS、Eudragit E，聚乙酸乙烯酯以及肠溶聚合物，或其混合物。

[0100] 示例性的崩解剂包括但不限于，低取代的羧甲基纤维素钠，交聚维酮（交联聚乙烯吡咯烷酮），羧甲基淀粉钠（淀粉乙醇酸钠），交联羧甲基纤维素钠（交联羧甲纤维素），预糊化淀粉（淀粉 1500），微晶纤维素，不溶于水的淀粉，羧甲基纤维素钙，低取代羟丙基纤维素，以及硅酸镁或硅酸铝。

[0101] 示例性的助流剂包括但不限于，镁、二氧化硅、滑石、淀粉、二氧化钛等。

[0102] 在又一个实施方式中，所述延长释放的制剂通过用包覆材料以及非必须的成孔物和其他赋形剂包覆含有水溶性 / 水分散性药物的颗粒而形成，所述颗粒如珠或珠群体（如上所述）。所述包覆材料优选选自纤维素聚合物，如乙基纤维素（例如，SURELEASE®）、甲基纤维素、羟丙基纤维素、羟丙基甲基纤维素、乙酸纤维素和醋酸邻苯二甲酸纤维素；聚乙烯醇；丙烯酸类聚合物，如聚丙烯酸酯、聚甲基丙烯酸酯及其共聚物；以及其它的基于水或基于溶剂的包覆材料。用于给定的珠的群体的控制释放包衣可以通过控制释放包衣的至少一个参数而控制，例如包衣的性能、包衣水平、成孔物类型以及浓度、工艺参数以及其组合。由此，通过改变参数（如成孔物浓度）或者固化条件，允许改变活性剂由任意给定的珠的群体释放，从而允许制剂有选择地调整为预定的释放曲线。

[0103] 在此，适合用在控制释放包衣中的成孔物可为有机或无机试剂，且包括能够在使用环境中从包衣溶解、提取或浸出的材料。示例性的成孔剂包括，但不限于，有机化合物，如单糖、寡糖和多糖，包括蔗糖、葡萄糖、果糖、甘露醇、甘露糖、半乳糖、山梨醇、支链淀粉、葡聚糖；在使用环境中可溶的聚合物，如水溶性亲水聚合物，羟基烷基纤维素，羧基烷基纤维素，羟丙基甲基纤维素，纤维素醚，丙烯酸类树脂，聚乙烯吡咯烷酮，交联聚乙烯吡咯烷酮，聚环氧乙烷，碳蜡（Carbowaxes），聚羧乙烯等，二醇，多元醇，多元醇，聚亚烷基二醇，聚乙二醇，聚丙二醇，或其嵌段聚合物，聚二醇，聚（α-Ω）亚烷基二醇；无机化合物，如碱金属盐类，碳酸锂、氯化钠、溴化钠、氯化钾、硫酸钾、磷酸钾、醋酸钠、柠檬酸钠、适当的钙盐、其组合物等。

[0104] 所述控制释放包衣可进一步包含本领域公知的其它添加剂，如增塑剂、抗粘剂、助流剂（或流动性助剂）以及消泡剂。

[0105] 在一些实施方式中，包覆的颗粒或珠可能另外包括“外包衣”，以提供例如，防潮、减少静电、味道掩蔽、调味、着色和 / 或磨光或其它对珠的装饰作用。对于这样的外包衣，合适的包衣材料是本领域公知的，且包括，但不限于，纤维素聚合物，如羟丙基甲基纤维素、羟丙基纤维素和微晶纤维素或其组合（例如，多种OPADRY®包衣材料）。

[0106] 包覆的颗粒或珠可额外包含增强剂，例如，其可示例性但不限制地为增强溶解剂、增强溶出剂、吸收促进剂、渗透促进剂、稳定剂、络合剂、酶抑制剂、P- 糖蛋白抑制剂以及多

药耐药蛋白抑制剂。或者，所述制剂也可包含与包衣的颗粒分开的增强剂，例如在单独的珠的群体中或者作为粉末。在又一个实施方式中，增强剂可以包含在包覆颗粒上的单独的层中，可以在控制释放包衣的下方或上方。

[0107] 在其他实施方式中，所述延长释放的制剂被配制为通过渗透机制释放活性剂。例如，胶囊可制成单渗透单元，或者其可包含 2、3、4、5 或 6 个封装在硬明胶胶囊内的推拉单元，藉此，每个双层推拉单元包含渗透推层和药物层，且两者都被半透膜包围。在与药物层相邻的膜上钻通一个或多个孔。这层膜可另外被依赖 pH 值的肠溶包衣覆盖，以防止释放，直到胃排空后。明胶胶囊在摄入后立即溶解。随着推拉单元进入小肠，肠溶包衣分解，然后让液体流动以通过半透膜，使渗透推部分溶胀，从而迫使药物以一定速率通过小孔，所述速率由水通过半透膜的速率而精确控制。药物的释放可以以恒定速率进行长达 24 小时以上。

[0108] 所述渗透推层包含一种或多种产生用于使水通过半透膜进入递送载体的核心的驱动力的渗透剂。一类渗透剂包括可水溶胀性亲水性聚合物，也被称为“渗透聚合物 (osmopolymers)”和“水凝胶”，其包括，但不限于，亲水性乙烯基和丙烯酸系聚合物，如海藻酸钙的多糖，聚氧化乙烯 (PEO)、聚乙二醇 (PEG)、聚丙二醇 (PPG)、聚 (甲基丙烯酸 2- 羟乙酯)、聚 (丙烯酸)、聚 (甲基丙烯酸)、聚乙烯吡咯烷酮 (PVP)、交联 PVP、聚乙烯醇 (PVA)、PVA/PVP 共聚物、具有如甲基丙烯酸甲酯和醋酸乙烯酯的疏水单体的 PVA/PVP 共聚物、含有大 PEO 嵌段的亲水性聚氨酯、交联甲羧纤维素钠、角叉藻聚糖、羟乙基纤维素 (HEC)、羟丙基纤维素 (HPC)、羟丙基甲基纤维素 (HPMC)、羧甲基纤维素 (CMC) 和羧乙基纤维素 (CEC)、海藻酸钠、聚卡波非、明胶、黄原胶和淀粉羟乙酸钠。

[0109] 另一类渗透剂包括酶原，其能够吸取水分以实现穿过半透膜的渗透压梯度。酶原的例子包括，但不限于，无机盐，如硫酸镁、氯化镁、氯化钙、氯化钠、氯化锂、硫酸钾、磷酸钾、碳酸钠、亚硫酸钠、硫酸锂、氯化钾、和硫酸钠 ；糖，如右旋糖 (dextrose)、果糖、葡萄糖 (glucose)、肌醇、乳糖、麦芽糖、甘露醇、棉子糖、山梨醇、蔗糖、海藻糖和木糖醇 ；有机酸，如抗坏血酸、苯甲酸、富马酸、柠檬酸、马来酸、癸二酸、山梨酸、己二酸、依地酸、谷氨酸、对甲苯磺酸、琥珀酸和酒石酸 ；尿素 ；以及它们的混合物。

[0110] 有助于形成半透膜的材料包括不同级别的丙烯酸树脂、乙烯树脂、醚类、聚酰胺类、聚酯类和纤维素衍生物，这些材料在生理相关的 pH 值下透水且不溶于水，或者，这些材料易于通过化学改变，例如交联而呈现不溶于水的性能。

[0111] 在一些实施方式中，所述延长释放的制剂可包括抵抗胃和肠内的侵蚀的多糖包衣。这种聚合物只能在包含了大量的微生物的结肠中降解，所述微生物含有可生物降解的酶，所述可生物降解的酶分解例如多糖包衣，从而以可控的依赖时间的方式释放药物内容物。示例性的多糖包衣可包括，例如，直链淀粉、阿拉伯半乳聚糖、壳聚糖、硫酸软骨素、环糊精、葡聚糖、瓜尔豆胶、果胶、木聚糖及其组合或衍生物。

[0112] 在一些实施方式中，本申请的药物组合物配制为延迟的延长释放型。在此使用的术语“延迟释放”是指一种不会立刻将活性成分崩解和释放到体内的药物治疗。在一些实施方式中，术语“延迟的延长释放”参照具有这样的释放曲线的药物制剂使用 ：所述释放曲线中，在施用后药物的释放中具有预设定的延迟。在一些实施方式中，延迟的延长释放制剂包括由肠溶包衣包覆的延长释放制剂，这是应用于口服药物的隔离，以防止在药物到达小肠之前释放。如肠溶包衣的延迟释放制剂防止对胃有刺激作用的药物 (如阿司匹林) 在胃

中溶解。这种包衣还用于保护对酸不稳定的药物，防止其暴露在胃的酸性环境中，而是将其递送到碱性 pH 环境中（肠道的 pH 值为 5.5 以上），在所述碱性环境下其不会降解，并给予他们所需的作用。

[0113] 术语“脉冲式释放”是延迟释放的一种，其在此参照以下使用：在预定的迟滞期以后，在短时期内立即提供迅速且瞬时的药物释放的药物制剂，从而产生在施用药物后药物的“脉冲”血浆分布。制剂可以被设计为在施用后预定的时间间隔下提供单脉冲式释放或多脉冲式释放，或者在一个时段的延长释放（例如，活性成分剩余部分的连续释放）后提供脉冲式释放（例如，活性成分的 20-60％）。

[0114] 延迟释放或脉冲式释放制剂通常包括一种或多种由隔离包衣覆盖的元件，其在一个特定的迟滞期以后溶解、侵蚀或破裂。在一些实施方式中，本申请的药物组合物被配制为延长释放或者延迟的延长释放，且其包含在单个单位剂量中施用的给定活性剂的总剂量的 100％。在其他实施方式中，所述药物组合物包含延长 / 延迟释放组分以及立即释放组分。在一些实施方式中，所述立即释放组分和延长 / 延迟释放组分含有相同的活性成分。在其它实施方式中，所述立即释放组分和延长 / 延迟释放组分含有不同的活性成分（例如，在一个组分中为镇痛剂，而在另一个组分中为 α - 阻滞剂）。在一些实施方式中，所述第一和第二组分各自包含 α - 阻滞剂和镇痛剂，所述镇痛剂选自阿司匹林、布洛芬、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚。在另外一些实施方式中，所述第一和第二组分各自包含 5α - 还原酶抑制剂和镇痛剂，所述 5α - 还原酶抑制剂选自非那雄胺、贝氯特来、依立雄胺、艾宗特来、拉匹雄胺和妥罗雄脲，以及所述镇痛剂自阿司匹林、布洛芬、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚。在另外一些实施方式中，所述延长 / 延迟释放组分由肠溶包衣包覆。在另外一些实施方式中，所述立即释放组分和 / 或延长 / 延迟释放组分进一步包括抗毒蕈碱剂，其选自奥昔布宁、索利那新、达非那新和阿托品。在另外一些实施方式中，所述立即释放组分和 / 或延长 / 延迟释放组分进一步包含抗利尿剂、抗毒蕈碱剂或二者的结合。在另外一些实施方式中，所述治疗方法包括在一个靶时间点（如就寝时间）之前至少 7 到 8 小时对受试者施用利尿剂，以及在该靶时间点前 2 小时内对所述受试者施用包含立即释放组分和 / 或延长 / 延迟释放组分的药物组合物。

[0115] 在其他实施方式中，“立即释放”组分提供将要通过药物制剂递送的活性剂的总剂量的约 5 至 50％，且“延长释放”组分可以提供将要通过药物制剂递送的活性剂的总剂量的约 50 至 95％。例如，立即释放组分提供将要通过药物制剂递送的活性剂的总剂量的约 20 至 60％，或约 20％、25％、30％、35％、40％、45％、50％、55％、60％。延长释放组分可以提供将要通过制剂递送的活性剂的总剂量的约 40％、45％、50％、55％、60％、65％、70％、75％或 80％。在一些实施方式中，延长释放组分进一步包括隔离包衣，以延迟活性剂的释放。

[0116] 根据目的，用于延迟释放的隔离包衣可以由各种不同的材料组成。此外，制剂可包括多个隔离包衣以助于以时间方式释放。该包衣可以是糖包衣、薄膜包衣（例如，基于羟丙基甲基纤维素、甲基纤维素、甲基羟乙基纤维素、羟丙基纤维素、羧甲基纤维素、丙烯酸酯共聚物、聚乙二醇和 / 或聚乙烯吡咯烷酮）、或基于甲基丙烯酸共聚物、邻苯二甲酸乙酸纤维素、羟丙基甲基纤维素邻苯二甲酸酯、羟丙基甲基纤维素醋酸酯琥珀酸酯、聚醋酸乙烯邻苯二甲酸酯、虫胶和 / 或乙基纤维素的包衣。此外，所述制剂可另外包括时间延迟材料，例如，单硬脂酸甘油酯或二硬脂酸甘油酯。

[0117] 在一些实施方式中，所述延迟的延长释放制剂包括肠溶包衣，所述肠溶包衣包含有助于活性剂在胃肠道的近端或远端区域中释放的一种或多种聚合物。在此使用的术语“肠溶聚合物包衣”是指包含具有依赖 pH 或者不依赖 pH 值释放曲线的一种或多种聚合物的包衣。通常情况下，包衣抵制在胃的酸性介质中的溶解，但在胃肠道的更远端的区域（如小肠或结肠）中会溶解或侵蚀。肠溶聚合物包衣通常抵制活性剂释放，直到在给药后约 3-4 小时的胃排空的迟滞期后的某时。

[0118] 依赖 pH 值的肠溶包衣包含一种或多种依赖 pH 值或对 pH 值敏感的聚合物，其能在较低 pH 值的条件下（如在胃部）保持它们的结构完整，而在胃肠道更远端的区域（如小肠）的较高 pH 值的环境下溶解，从而释放出药物内容物。对于本发明的目的，“依赖 pH 值”被定义为具有根据环境 pH 值而变化的特性（例如，溶解）。示例性的依赖 pH 值的聚合物包括，但不限于，甲基丙烯酸共聚物、甲基丙烯酸 - 甲基丙烯酸甲酯共聚物（如德国 Rohm 股份有限公司的 EUDRAGIT® L100(A 型）、EUDRAGIT® S100(B 型））；甲基丙烯酸 - 丙烯酸乙酯共聚物（如德国 Rohm 股份有限公司的 EUDRAGIT® L100-55(C 型）和 EUDRAGIT® L30D-55 共聚物分散体）；甲基丙烯酸 - 甲基丙烯酸甲酯和甲基丙烯酸甲酯的共聚物（EUDRAGIT® FS）；甲基丙烯酸、甲基丙烯酸酯和丙烯酸乙酯的三元共聚物；邻苯二甲酸乙酸纤维素 (CAP)；羟丙基甲基纤维素邻苯二甲酸酯 (HPMCP)（例如，日本信越化学的 HP-55、HP-50、HP-55S）；聚醋酸乙烯邻苯二甲酸酯 (PVAP)（例如，COATERIC®、OPADRY® 肠道白 (enteric white)OY-P-7171）；醋酸纤维素琥珀酸酯 (CAS)；羟丙基甲基纤维素醋酸酯琥珀酸酯 (HPMCAS)，例如，HPMCAS LF 级、MF 级、HF 级，包括 AQOAT® LF 和 AQOAT® MF（日本信越化学）；日本信越化学）；虫胶（例如，Marcoat™125 和 Marcoat™125N）；羧甲基乙基纤维素 (CMEC，Freund 公司，日本）、邻苯二甲酸乙酸纤维素 (CAP)（例如，AQUATERIC®）；乙酸 -1,2,4- 苯三酸纤维素 (CAT)；以及重量比在约 2 ：1 至约 5 ：1 的其两种或更多种的混合物，例如，重量比为约 3 ：1 至约 2 ：1 的 EUDRAGIT® L100-55 和 EUDRAGIT® S100 的混合物，或重量比为约 3 ：1 至约 5 ：1 的 EUDRAGIT® L30D-55 和 EUDRAGIT® FS 的混合物。

[0119] 依赖 pH 值的聚合物通常显示出特有的对于溶解的最适 pH 值。在一些实施方式中，依赖 pH 的聚合物显示出在约 5.0 和 5.5 之间、约 5.5 和 6.0 之间、约 6.0 和 6.5 之间或约 6.5 和 7.0 之间的最适 pH 值。在另一些的实施方式中，依赖 pH 的聚合物显示出≥ 5.0、≥ 5.5、≥ 6.0、≥ 6.5 或≥ 7.0 的最适 pH 值。

[0120] 在一些实施方式中，包衣方法采用一种或多种依赖 pH 值和一种或多种不依赖 pH 值的聚合物的混合。一旦可溶性聚合物到达了其溶解的最适 pH 值，依赖 pH 值和不依赖 pH 值的聚合物的混合可以减小活性成分的释放速率。

[0121] 在一些实施方式中，“时间控制的”或“依赖时间的”释放曲线可以使用包含一种或多种活性剂的不溶于水的胶囊体而获得，其中，所述胶囊体在其一端以不溶的、但可渗透的且可溶胀的水凝胶塞封闭。当与胃肠液或溶解介质接触时，所述塞溶胀，将其自身推出胶

囊，并在预定的延滞时间（该时间可通过，例如，塞的位置和尺寸来控制）以后，释放药物。所述胶囊体可以进一步由保持胶囊完整的外部的依赖 pH 值的肠溶包衣包覆，直到其到达小肠。合适的塞的材料包括，例如，聚甲基丙烯酸酯类、可侵蚀的压缩聚合物（例如，HPMC，聚乙烯醇）、凝结的熔融聚合物（如甘油单油酸酯）和酶控制的可侵蚀的聚合物（例如，多糖，如直链淀粉、阿拉伯半乳聚糖、壳聚糖、硫酸软骨素、环糊精、葡聚糖、瓜尔豆胶、果胶和木聚糖）。

[0122] 在另一些的实施方式中，胶囊或双层片可配制为包括含有药物的核，其由溶胀层以及外部不溶但可半渗透的聚合物包衣或膜覆盖。在破裂前的延滞时间可通过聚合物包衣的渗透和机械性能以及溶胀层的溶胀行为所控制。通常，溶胀层包含一种或多种溶胀剂，如溶胀且在其结构中保留水分的可溶胀的亲水聚合物。

[0123] 示例性的在延迟释放的包衣中使用的可水溶胀的材料包括，但不限于，聚环氧乙烷（例如，平均分子量为 1,000,000 至 7,000,000，例如，POLYOX®）、甲基纤维素、羟丙基纤维素、羟丙基甲基纤维素；重均分子量为 100,000 至 6,000,000 的聚环氧烷，包括但不限于聚甲醛 (poly(methylene oxide))、聚环氧丁烷；分子量为 25,000 至 5,000,000 的聚（甲基丙烯酸羟烷基酯）；与乙二醛、甲醛或戊二醛交联、具有低级缩醛残基且聚合度为 200 至 30,000 的聚乙烯醇；甲基纤维素、交联琼脂和羧甲基纤维素的混合物；形成水凝胶的共聚物，其通过以下制备：形成极细分开的马来酸酐与苯乙烯、乙烯、丙烯、丁烯或异丁烯的共聚物的分散体，其在共聚物中以每摩尔马来酸酐 0.001 至 0.5 摩尔的饱和交联剂交联；分子量为 450,000 至 4,000,000 的 CARBOPOL® 酸性羧基聚合物；CYANAMER® 聚丙烯酰胺；交联的水可溶胀的茚马来酸酐聚合物；分子量为 80,000 至 200,000 的 GOODRITE® 聚丙烯酸；淀粉接枝共聚物；由缩合的葡萄糖单元（如二酯交联的聚葡聚糖）组成的 AQUA-KEEPS® 丙烯酸酯聚合物多糖；0.5％至 1％ w/v 水溶液下粘度为 3,000 至 60,000mPa 的卡波姆；纤维素醚，如 1％ w/w 水溶液 (25℃) 下粘度约 1,000 至 7,000mPa 的羟丙基纤维素；2％ w/v 水溶液下粘度为约 1000 以上、优选 2,500 以上、最高至 25,000mPa 的羟丙基甲基纤维素；在 20℃，10％ w/v 水溶液下粘度为约 300 至 700mPa 的聚乙烯吡咯烷酮；以及它们的混合物。

[0124] 或者，药物的释放时间可通过崩解延滞时间来控制，所述崩解延滞时间取决于不溶于水的聚合物膜（如乙基纤维素，EC）的耐受性和厚度之间的平衡，所述不溶于水的聚合物膜包含在主体底部的预定的微孔，以及一定量的可溶胀的辅料，如低级取代的羟丙基纤维素 (L-HPC) 和乙醇酸钠。口服给药后，胃肠液渗透通过微孔，造成可溶胀的辅料的溶胀，这样产生使胶囊部分崩解的内部压力，所述胶囊部分包括含有可溶胀的材料的第一胶囊体、含有药物的第二胶囊体和附着在第一胶囊体上的外盖。

[0125] 肠溶层可进一步包含抗粘剂，如滑石或甘油单硬脂酸酯和 / 或增塑剂。肠溶层可进一步包含一种或多种增塑剂，所述增塑剂包括，但不仅限于，柠檬酸三乙酯、柠檬酸乙酰基三乙酯、柠檬酸乙酰基三丁酯、聚乙二醇乙酰化甘油一酯、甘油、三醋酸甘油酯、丙二醇、邻苯二甲酸酯（如邻苯二甲酸二乙酯、邻苯二甲酸二丁酯）、二氧化钛、氧化铁、蓖麻油、山梨醇和癸二酸二丁酯。

[0126] 在另一个实施方式中，延迟释放制剂采用了透水但不溶的薄膜包衣以封装活性成分以及渗透剂。随着水从肠道通过薄膜慢慢扩散进入核，所述核溶胀直到膜破裂，从而释放活性成分。可以调整膜包衣，以获得不同速率的水渗透或释放时间。

[0127] 在另一个实施方式中，延迟释放制剂采用了不透水的片状包衣，藉此，水通过包衣中的控制孔进入，直到核突然破裂。当片剂突然破裂时，药物内容物立即释放，或者经过较长的时间释放。可修改这些和其他技术，以在药物开始释放前允许形成预定的迟滞期。

[0128] 在另一个实施方式中，活性剂以制剂形式被递送，从而提供延迟释放和延长释放（延迟－持续）。术语“延迟－延长－释放”在此参照以下使用：在施用后的一个预定的时间或者迟滞期，提供活性剂的脉冲式释放的药物制剂，然后是活性剂的延长释放。

[0129] 在一些实施方式中，立即释放、延长释放、延迟释放或延迟－延长－释放制剂包括活性核，所述活性核由一种或多种惰性粒子组成，所述惰性粒子各自以其表面上包被有药物（例如，以含药物的成膜组合物的形式（使用例如流化床技术或本领域的技术人员公知的其他方法））的珠、丸剂、药丸、颗粒粒子、微胶囊、微球、微颗粒、纳米胶囊或纳米球的形式。所述惰性粒子可以是不同大小的，只要其足够大而保持不易溶解。或者，所述活性核可以通过含有药物成分的聚合物组合物的造粒和碾磨和／或通过挤出和滚圆来制备。

[0130] 在所述核中的药物量将取决于所需要的剂量，且通常从约 5 至 90wt％变化。通常，基于包衣粒子的重量，根据所需的延滞时间和释放曲线的类型和／或所选择的聚合物和包衣溶剂，在活性核上的聚合物包衣将为约 1 至 50％。本领域的技术人员将能够选择合适量的在核上包被或引入核以实现所需的剂量的药物。在一个实施方式中，无活性的核心可以是糖球或缓冲晶体或封装缓冲晶体，如碳酸钙、碳酸氢钠、富马酸、酒石酸等，它们改变药物的微环境以促进其释放。

[0131] 在一些实施方式中，例如，延迟释放或延迟－延长释放组合物可以是通过以不溶于水的聚合物和肠溶聚合物的混合物包覆水溶性／可分散的含药颗粒（如珠）形成，其中，不溶于水的聚合物和肠溶聚合物可以 4 ： 1 至 1 ： 1 的重量比存在，且基于包覆的珠的总重量，包衣的总重量为 10 至 60wt％。药物分层的珠可非必须地包括控制内溶出率的乙基纤维素膜。优化外层的组合物，以及聚合物膜的内层和外层的单独的重量，以对于给定的活性实现理想的昼夜节律释放曲线，这基于体外／体内的相关性而预计得到。

[0132] 在另一些实施方式中，所述制剂可包含含有立即释放的药物的颗粒（没有控制溶出速率的聚合物膜）以及延迟－延长释放的珠（其显示出，例如在口服施药以后 2 至 4 小时的延滞时间）的混合物，从而提供双脉冲释放曲线。

[0133] 在一些实施方式中，所述活性核由一种或多种控制溶出速率的聚合物的层包覆，从而获得理想的释放曲线（有或没有延滞时间）。内层膜可以在吸取水或体液进入核后在很大程度上控制药物释放速率，而外层膜可以提供所需的延滞时间（在吸取水或体液进入核后没有或几乎没有药物释放的时期）。内层膜可包括不溶于水的聚合物，或不溶于水的聚合物和水溶性聚合物的混合物。

[0134] 如上所述，在很大程度上控制延滞时间最长达 6 小时的适合于外膜的聚合物包括肠溶聚合物，以及 10 至 50wt％的不溶于水的聚合物。不溶于水的聚合物与肠溶聚合物的比可从 4 ： 1 至 1 ： 2 变化，优选所述聚合物以约 1 ： 1 的比例存在。通常使用的不溶于水的聚合物为乙基纤维素。

[0135] 不溶于水的聚合物的例子包括乙基纤维素、聚醋酸乙烯酯（来自BASF的Kollicoat SR#0D)、基于丙烯酸乙酯和甲基丙烯酸甲酯的中性共聚物、具有季铵基团的丙烯酸酯和甲基丙烯酸酯的共聚物（如EUDRAGIT® NE、RS和RS30D、RL或RL30D等）。水溶性聚合物的例子包括低分子量的HPMC；HPC；甲基纤维素；聚乙二醇（分子量>3000的PEG)，根据在水和溶剂中的活性的溶解度，或者基于所使用的包覆制剂的乳液悬浮液，其范围从1wt％高至10wt％。不溶于水的聚合物与水溶性聚合物的比可通常从95 ： 5至60 ： 40，优选从80 ： 20至65 ： 35变化。

[0136] 在一些实施方式中，使用AMBERLITETM IRP69树脂作为延长释放的载体。AMBERLITE™ IRP69是一种不溶的强酸性钠型阳离子交换树脂，其适合作为阳离子（碱性）物质的载体。在其他实施方式中，使用DUOLITE™ AP143/1093树脂作为延长释放的载体。DUOLITE™ AP143/1093是一种不溶的强碱性阴离子交换树脂，其适合作为阴离子（酸性）物质的载体。

[0137] 当作为药物载体使用时，AMBERLITE IRP69或/和DUOLITE™ AP143/1093树脂提供了向不溶性聚合物基质上粘合药剂的方法。通过形成树脂-药物复合物（药物树脂酸盐（酯））实现延长释放。随着药物与高电解质浓度达到平衡，药物在体内从树脂中释放，这是典型的胃肠道药物释放。由于与阳离子交换系统的芳香结构的疏水相互作用，通常，更多的疏水性药物会以较低的速率从树脂中洗脱。

[0138] 多数肠道包衣通过呈现在较高的酸性pH条件（即胃中的条件）下稳定，但在较低的酸性pH条件（相对而言更高碱性）下分解的表面而工作。因此，肠溶包衣的药丸不溶于酸性胃液中(pH值～3)，但它们会溶于小肠中存在的碱性环境(pH值7-9)。肠溶包衣材料的例子包括，但不仅限于，丙烯酸甲酯-甲基丙烯酸共聚物、醋酸纤维素琥珀酸酯、羟丙基甲基纤维素邻苯二甲酸酯、羟丙基甲基纤维素醋酸琥珀酸酯（羟丙甲纤维素醋酸琥珀酸酯）、聚醋酸乙烯邻苯二甲酸酯(PVAP)、甲基丙烯酸甲酯-甲基丙烯酸共聚物、海藻酸钠和硬脂酸。在一些实施方式中，所述药物组合物被配制为口服施用。口服剂形包括，例如片剂、胶囊、锭剂，并且也可以包括多个可被胶囊封装或者不被胶囊封装颗粒、珠、粉末或丸剂。片剂和胶囊代表最方便的口服剂型，在此情况下使用固体的药物载体。

[0139] 在延迟释放制剂中，可以向丸剂、片剂或胶囊应用一个或多个隔离包衣，以助于减缓药物在肠道中的溶解和相伴释放。通常情况下，隔离包衣包含一种或多种聚合物，在药物组合物或活性核周围，包围、围绕或形成层或膜。

[0140] 在一些实施方式中，在制剂中活性剂被递送，从而在施用后的预定的时间提供延迟释放。延迟可能高达约10分钟、约20分钟、约30分钟、约1小时、约2小时、约3小时、约4小时、约5小时、约6小时或更长的时间。

[0141] 不同的包衣技术可应用于含有活性剂的颗粒、珠、粉末或丸剂、片剂、胶囊或其结合，以产生不同的和区别的释放曲线。在一些实施方式中，药物组合物是以包含单包衣层的片剂或胶囊的形式。在另一些实施方式中，药物组合物是以包含多包衣层的片剂或胶囊的形式。

[0142] 在一些实施方式中，所述药物组合物包含一种或多种镇痛剂、一种或多种α-阻滞剂以及一种或多种选自抗毒蕈碱剂、抗利尿剂和解痉剂的其他活性成分。在一些实施方式中，所述药物组合物包含一种或多种镇痛剂、一种或多种5α-还原酶抑制剂以及一种或

多种选自抗毒蕈碱剂、抗利尿剂、α－阻滞剂和解痉剂的其他活性成分。抗毒蕈碱剂的例子包括，但不限于：奥昔布宁、索菲那（solifenacin）、达非那新和阿托品。抗利尿剂的例子包括，但不限于，抗利尿激素（ADH）、血管紧张素Ⅱ、醛固酮、血管加压素、血管加压素类似物（例如，去氨加压素精氨加压素、赖氨加压素、苯赖加压素、鸟氨加压素、特利加压素）；血管加压素受体激动剂、心房利钠肽（ANP）和C型利钠肽（CNP）受体（即，NPR1、NPR2、NPR3）拮抗剂（例如，HS-142-1、靛红、[Asu7,23']b-ANP-(7-28)]、安南汀（anantin）、来自天蓝色链霉菌（Streptomyces coerulescens）的环肽，以及3G12单克隆抗体）；促生长素抑制素2型受体拮抗剂（如，促生长素抑制素），及其药学上可接受的衍生物、类似物、盐、水合物和溶剂合物。解痉剂的例子包括，但不限于，卡立普多、苯（并）二氮卓类、巴氯芬、环苯扎珠、美他沙酮、美索巴莫、可乐定、可乐定类似物和丹曲洛林。

[0143] 在一些实施方式中，所述药物组合物包含一种或多种镇痛剂以及一种或多种α－阻滞剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种α－阻滞剂，和（3）一种或多种抗毒蕈碱剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种α－阻滞剂和（3）一种或多种抗利尿剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种α－阻滞剂和（3）一种或多种解痉剂。在另外一些实施方式中，所述药物组合物包含1）一种或两种镇痛剂，（2）一种或多种α－阻滞剂，（3）一种或两种抗毒蕈碱剂和（4）一种或两种抗利尿剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种α－阻滞剂，（3）一种或多种解痉剂和（4）一种或多种抗利尿剂。

[0144] 在一些实施方式中，所述药物组合物包含一种或多种镇痛剂以及一种或多种5α－还原酶抑制剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种5α－还原酶抑制剂，（3）一种或多种抗毒蕈碱剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种5α－还原酶抑制剂和（3）一种或多种抗利尿剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种5α－还原酶抑制剂和（3）一种或多种解痉剂。在另外一些实施方式中，所述药物组合物包含（1）一种或两种镇痛剂，（2）一种或多种5α－还原酶抑制剂，（3）一种或两种抗毒蕈碱剂和（4）一种或两种抗利尿剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种5α－还原酶抑制剂，（3）一种或多种解痉剂和（4）一种或多种抗利尿剂。

[0145] 在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种5α－还原酶抑制剂和（3）一种或多种α－阻滞剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种5α－还原酶抑制剂，（3）一种或多种α－阻滞剂和（4）一种或多种抗利尿剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种5α－还原酶抑制剂，（3）一种或多种α－阻滞剂和（4）一种或多种解痉剂。在另外一些实施方式中，所述药物组合物包含（1）一种或两种镇痛剂，（2）一种或多种5α－还原酶抑制剂，（3）一种或两种抗毒蕈碱剂，（4）一种或两种抗利尿剂和（5）一种或多种α－阻滞剂。在另外一些实施方式中，所述药物组合物包含（1）一种或多种镇痛剂，（2）一种或多种5α－还原酶抑制剂，（3）一种或多种解痉剂，（4）一种或多种抗利尿剂和（5）一种或多种α－阻滞剂。

[0146] 在一个实施方式中，多数活性成分被配制为立即释放。在另外一些实施方式中，多数活性成分被配制为延长释放。在另外一些实施方式中，多数活性成分被配制为立即释放和延长释放（例如，每个活性成分的第一部分被配制成立即释放，而每个活性成分的第二部分被配制成延长释放）。在又一个实施方式中，多数活性成分中的一些被配制为立即释放，而多数活性成分中的一些被配制为延长释放（例如，活性成分 A，B，C 被配制为立即释放，而活性成分 C 和 D 被配制为延长释放）。在另外的一些实施方式中，立即释放组分和 / 或延长释放组分被进一步包覆上延迟释放包衣（如肠溶包衣）。

[0147] 在某些实施方式中，所述药物组合物包含立即释放组分和延长释放组分。该立即释放组分可包含一种或多种选自镇痛剂、α - 阻滞剂、5α - 还原酶抑制剂、抗毒蕈碱剂、抗利尿剂和解痉剂的活性成分。该延长释放组分可包含一种或多种选自镇痛剂、α - 阻滞剂、抗毒蕈碱剂、抗利尿剂和解痉剂的活性成分。在一些实施方式中，该立即释放组分和延长释放组分恰好具有相同的活性成分。在另外一些实施方式中，该立即释放组分和延长释放组分具有不同的活性成分。在另外一些实施方式中，该立即释放组分和延长释放组分具有一种或多种共同的活性成分。在一些实施方式中，立即释放组分和 / 或延长释放组分被进一步包覆上延迟释放包衣（如肠溶包衣）。

[0148] 在一个实施方式中，所述药物组合物包含两种或更多种被配制成在大约相同的时间立即释放的活性成分（例如，一种或多种镇痛剂和一种或多种 α - 阻滞剂、一种或多种 5α - 还原酶抑制剂、一种或多种抗毒蕈碱剂或抗利尿剂或解痉剂的混合物）。在另一个实施方式中，所述药物组合物包含两种或更多种被配制成在大约相同的时间延长释放的活性成分。在另一个实施方式中，所述药物组合物包含两种或更多种活性成分，该活性成分被配制成两种延长释放组分，每一种延长释放组分提供一个不同的延长释放曲线。例如，第一延长释放组分在第一释放速率下释放第一活性成分，而第二延长释放组分在第二释放速率下释放第二活性成分。在另一个实施方式中，所述药物组合物包含两种或更多种均被配制为延迟释放的活性成分。在另一个实施方式中，所述药物组合物包含两种或更多种被配制为延迟释放的活性成分。在另一个实施方式中，所述药物组合物包含两种或更多种被配制成两种延迟释放组分的活性成分，每一种延迟释放组分提供一个不同的延迟释放曲线。例如，第一延迟释放组分在第一时间点释放第一活性成分，而第二延迟释放组分在第二时间点释放第二活性成分。在另一个实施方式中，所述药物组合物包含两种或更多种活性成分，其中的一种或多种被配制成立即释放，而其余的被配制成延长释放。在另一个实施方式中，所述药物组合物包含两种或更多种活性成分，其中一部分被配制成立即释放，而剩余部分被配制成延长释放。

[0149] 在一些实施方式中，所述药物组合物包含一种或多种镇痛剂，和一种或多种 α - 阻滞剂、5α - 还原酶抑制剂、抗利尿剂，其中，所述一种或多种镇痛剂和一种或多种 α - 阻滞剂被配制成延迟释放，以及其中，所述抗利尿剂被配制成立即释放。在其他的实施方式中，所述药物组合物进一步包含选自镇痛剂、α - 阻滞剂、5α - 还原酶抑制剂、抗毒蕈碱剂、抗利尿剂和解痉剂的附加剂，其中，所述附加剂被配制成延迟释放。在一些实施方式中，延迟释放制剂延迟活性成分的释放达 1、2、3、4 或 5 小时。

[0150] 在此使用的术语“立即释放”参照不含有溶解速率控制材料的药物制剂。在施用立即释放的制剂以后，活性剂的释放基本没有延迟。立即释放的包衣可包括施用后立即溶

解从而释放其中的药物内容物的合适的材料。立即释放包衣材料的例子包括明胶，聚乙烯醇聚乙二醇 (PVA-PEG) 共聚物（如 KOLLICOAT® ）和本领域技术人员公知的各种其他材料。

[0151] 立即释放的组合物可包括在单一单位剂量中施用的给定的活性剂的总剂量的100％。或者，立即释放组分可以在联合的释放曲线制剂中作为一个组分而包含于其中，所述联合的释放曲线制剂可以提供将要通过药物制剂递送的活性剂的总剂量的约 1％至约60％。例如，立即释放组分可以提供将要通过制剂递送的活性剂的总剂量的约 5％ -60％、约 10％至约 60％、约 10％至约 50％、约 10％至约 40％、约 10％至约 30％、约 10％至约20％、约 20％至约 60％、约 20％至约 50％、约 20％至约 30％、约 30％至约 60％、约 30％至约 50％、约 40％至约 60％、约 40％至约 50％、约 45％至约 60％或约 45％至约 50％。在另外一些实施方式中，立即释放组分提供将要通过制剂递送的活性剂的总剂量的约 2、4、5、10、15、20、25、30、35、40、45、50、55 或 60％。

[0152] 在一些实施方式中，立即释放或延迟释放制剂包括活性核，所述活性核由一种或多种惰性粒子组成，所述惰性粒子各自以其表面上包被有药物（例如，以含药物的成膜组合物的形式（使用例如流化床技术或本领域的技术人员公知的其他方法））的珠、丸剂、药丸、颗粒粒子、微胶囊、微球、微颗粒、纳米胶囊或纳米球的形式。所述惰性粒子可以是不同大小的，只要其足够大而保持不易溶解即可。或者，所述活性核可以通过含有药物成分的聚合物组合物的造粒和碾磨和 / 或通过挤出和滚圆来制备。

[0153] 在所述核中的药物量将取决于所需要的剂量，且通常从约 5 至 90wt％变化。通常，基于包衣粒子的重量，根据所需的延滞时间和释放曲线的类型和 / 或所选择的聚合物和包衣溶剂，在活性核上的聚合物包衣将为约 1 至 50％。本领域的技术人员将能够选择合适量的在核上包被或引入核的药物以实现所需的剂量。在一个实施方式中，无活性的核心可以是糖球或缓冲晶体或封装缓冲晶体，如碳酸钙、碳酸氢钠、富马酸、酒石酸等，它们改变药物的微环境以促进其释放。

[0154] 在一些实施方式中，延迟释放制剂是通过以不溶于水的聚合物和肠溶聚合物的混合物包覆水溶性 / 可分散的含药物的颗粒（如珠）而形成，其中，不溶于水的聚合物和肠溶聚合物可以 4 ： 1 至 1 ： 1 的重量比存在，且基于包覆的珠的总重量，包衣的总重量为 10 至60wt％。药物分层的珠可非必须地包括控制内溶出率的乙基纤维素膜。优化外层的组合物，以及聚合物膜的内层和外层的单独的重量，以对于给定的活性实现理想的昼夜节律释放曲线，这基于体外 / 体内的相关性而预计得到。

[0155] 在另一些实施方式中，所述制剂包含含有立即释放药物的颗粒（没有控制溶出速率的聚合物膜）和延迟释放的珠（其显示出，例如在口服施药以后 2 至 4 小时的延滞时间）的混合物，从而提供双脉冲释放曲线。在另一些实施方式中，所述制剂包括两种类型的延迟释放珠的混合物 :显示出 1 至 3 小时延滞时间的第一种类型和显示出 4 至 6 小时延滞时间的第二种类型。

[0156] 优选地，制剂被设计为具有这样的释放曲线 :能够限制其对安静睡眠的干扰，其中，所述制剂在个体通常被排尿冲动唤醒时释放药物。例如，考虑到通常在晚上 11 点开始睡眠且通常在凌晨 12:30、凌晨 3:00 和清晨 6:00 被唤醒排尿的个体。延迟的延长释放载体能够在晚上 10 点服用，并在凌晨 12 点开始递送药物并在 5-8 小时的时段内逐渐地释放

药物，藉此推迟或消除排尿需求。在另外一些实施方式中，制剂被设计为具有这样的释放曲线：药物的一部分（例如，20-60％）在施用后立即或2小时之内释放，剩余部分的在延长的时段内释放。所述药物组合物可以日常施用或根据需要施用。在某些实施方式中，所述药物组合物被睡前施用于受试者。在一些实施方式中，所述药物组合物在睡前立即施用。在一些实施方式中，所述药物组合物在睡前大约两小时之内，优选睡前大约一小时之内施用。在另一个实施方式中，所述药物组合物在睡前大约两小时施用。在一个进一步的实施方式中，所述药物组合物在睡前至少两小时施用。在另一个实施方式中，所述药物组合物在睡前大约一小时施用。在一个进一步的实施方式中，所述药物组合物在睡前至少一小时施用。在一个更进一步的实施方式中，所述药物组合物在睡前少于一小时施用。在另一个更进一步的实施方式中，所述药物组合物在睡前立即施用。优选地，所述药物组合物口服施用。合适的口服施用组合物包括，但不限于：片剂、包衣片剂、锭剂、胶囊、粉剂、颗粒和可溶片剂，以及液体形式（例如，混悬剂、分散剂或溶液剂）。

[0157] 在立即释放组分或延长释放组分中的活性剂的合适的剂量（“治疗有效量”），将取决于例如病情的严重程度和进程，施药方式、特别制剂的生物利用度、病人的年龄和体重、病人的临床病史和对活性剂的反应、医嘱，等等。

[0158] 通常建议，无论一次或多次施用，立即释放组分、延长释放组分或延迟-延长-释放组分中的活性剂的治疗有效量在约100μg/kg体重/日至约100mg/kg体重/日的范围内施用。在一些实施方式中，以单剂或多剂每日施用的各活性剂的范围在约100μg/kg体重/日至约50mg/kg体重/日、100μg/kg体重/日至约10mg/kg体重/日、100μg/kg体重/日至约1mg/kg体重/日、100μg/kg体重/日至约10mg/kg体重/日、500μg/kg体重/日至约100mg/kg体重/日、500μg/kg体重/日至约50mg/kg体重/日、500μg/kg体重/日至约5mg/kg体重/日、1mg/kg体重/日至约100mg/kg体重/日、1mg/kg体重/日至约50mg/kg体重/日、1mg/kg体重/日至约10mg/kg体重/日、5mg/kg体重/日至约100mg/kg体重/日、5mg/kg体重/日至约50mg/kg体重/日、10mg/kg体重/日至约100mg/kg体重/日和10mg/kg体重/日至约50mg/kg体重/日。

[0159] 此处所述的活性剂可被包含在日常单剂或多剂口服施用的立即释放组分或延长释放组分、延迟-延长释放组分或其联合中，该单剂或多剂的范围在1mg至2000mg，5mg至2000mg，10mg至2000mg，50mg至2000mg，100mg至2000mg，200mg至2000mg，500mg至2000mg，5mg至1800mg，10mg至1600mg，50mg至1600mg，100mg至1500mg，150mg至1200mg，200mg至1000mg，300mg至800mg，325mg至500mg，1mg至1000mg，1mg至500mg，1mg至200mg，5mg至1000mg，5mg至500mg，5mg至200mg，10mg至1000mg，10mg至500mg，10mg至200mg，50mg至1000mg，50mg至500mg，50mg至200mg，250mg至1000mg，250mg至500mg，500mg至1000mg，500mg至2000mg。正如所料，所述剂量将取决于患者的病情、尺寸、年龄和病情。

[0160] 在一些实施方式中，所述药物组合物包含单一镇痛剂，和一种或多种α-阻滞剂或一种或多种5α-还原酶抑制剂。在一个实施方式中，所述单一镇痛剂是阿司匹林。在另一个实施方式中，所述单一镇痛剂是布洛芬。在另一个实施方式中，所述单一镇痛剂是萘普生或萘普生钠。在另一个实施方式中，所述单一镇痛剂是吲哚美辛。在另一个实施方式中，所述单一镇痛剂是萘丁美酮。在另一个实施方式中，所述单一镇痛剂是对乙酰氨基酚。在另

一个实施方式中，所述单一镇痛剂是对乙酰氨基酚以及所述一种或多种 α－阻滞剂包含坦洛新。在另一个实施方式中，所述单一镇痛剂是对乙酰氨基酚以及所述一种或多种 5α－还原酶抑制剂包含非那雄胺。

[0161] 在一些实施方式中，所述单一镇痛剂以每日 1mg 至 2000mg，5mg 至 2000mg，20mg 至 2000mg，5mg 至 1000mg，20mg 至 1000mg，50mg 至 500mg，100mg 至 500mg，250mg 至 500mg，250mg 至 1000mg 或 500mg 至 1000mg 的剂量给予。在某些实施方式中，所述药物组合物包含作为单一镇痛剂的乙酰水杨酸、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮或对乙酰氨基酚，并且所述镇痛剂以 5mg 至 2000mg，20mg 至 2000mg，5mg 至 1000mg，20mg 至 1000mg，50mg 至 500mg，100mg 至 500mg，250mg 至 500mg，250mg 至 1000mg 或 500mg 至 1000mg 的每日剂量范围口服施用。在一些实施方式中，以 1mg 至 2000mg，5mg 至 2000mg，20mg 至 2000mg，5mg 至 1000mg，20mg 至 1000mg，50mg 至 500mg，100mg 至 500mg，250mg 至 500mg，250mg 至 1000mg 或 500mg 至 1000mg 的每日剂量给予第二镇痛剂。

[0162] 在另一些实施方式中，所述药物组合物包括一对镇痛剂和一种或多种 α－阻滞剂。这种配对的镇痛剂的例子包括，但不限于，乙酰水杨酸和布洛芬、乙酰水杨酸和萘普生钠、乙酰水杨酸和萘丁美酮、乙酰水杨酸和对乙酰氨基酚、乙酰水杨酸和吲哚美辛、布洛芬和萘普生钠、布洛芬和萘丁美酮、布洛芬和对乙酰氨基酚、布洛芬和吲哚美辛、萘普生、萘普生钠和萘丁美酮、萘普生钠和对乙酰氨基酚、萘普生钠和吲哚美辛、萘丁美酮和对乙酰氨基酚、萘丁美酮和吲哚美辛、以及对乙酰氨基酚和吲哚美辛。所述配对的镇痛剂以 0.1 ： 1 至 10 ： 1、0.2 ： 1 至 5 ： 1 或 0.3 ： 1 至 3 ： 1 的重量比混合，组合剂量范围在 5mg 至 2000mg，20mg 至 2000mg，100mg 至 2000mg，200mg 至 2000mg，500mg 至 2000mg，5mg 至 1500mg，20mg 至 1500mg，100mg 至 1500mg，200mg 至 1500mg，500mg 至 1500mg，5mg 至 1000mg，20mg 至 1000mg，100mg 至 1000mg，250mg 至 500mg，250mg 至 1000mg，250mg 至 1500mg，500mg 至 1000mg，500mg 至 1500mg，1000mg 至 1500mg， 和 1000mg 至 2000mg。在一个实施方式中，所述配对的镇痛剂以 1 ： 1 的重量比混合。

[0163] 在另一些实施方式中，本申请的所述药物组合物进一步包含一种或多种抗毒蕈碱剂。所述抗毒蕈碱剂的例子包括，但不限于奥昔布宁、索非那新、达非那新、非索罗定、托特罗定、曲司氯铵和阿托品。抗毒蕈碱剂的日常剂量范围在 0.01mg 至 100mg，0.1mg 至 100mg，1mg 至 100mg，10mg 至 100mg，0.01mg 至 25mg，0.1mg 至 25mg，1mg 至 25mg，10mg 至 25mg，0.01mg 至 10mg，0.1mg 至 10mg，1mg 至 10mg，10mg 至 10mg 和 10mg 至 25mg。

[0164] 在某些实施方式中，所述药物组合物包含一种或多种 α－阻滞剂、选自乙酰水杨酸、布洛芬、萘普生、萘普生钠、萘丁美酮、对乙酰氨基酚和吲哚美辛的镇痛剂，以及选自奥昔布宁、索非那新、达非那新和阿托品的抗毒蕈碱剂。

[0165] 本申请的另一方面涉及通过向需要其的人施用以立即释放制剂配制的药物组合物从而缓解尿频的方法。所述药物组合物包含一种或多种镇痛剂和一种或多种选自 5α－还原酶抑制剂、α－阻滞剂、抗毒蕈碱剂、抗利尿剂和解痉剂的附加活性成分。所述药物组合物可被配制为片剂、胶囊剂、锭剂、粉剂、颗粒、液体、凝胶或乳液的形式。所述液体、凝胶或乳液可由受试者以直接形式或者包含在胶囊中的形式摄入。

[0166] 在一些实施方式中，所述镇痛剂选自以下物质：水杨酸盐、阿司匹林、水杨酸、水杨酸甲酯、二氟尼柳、双水杨酯、奥沙拉秦、柳氮磺吡啶、对氨基苯酚的衍生物、乙酰苯胺、对

乙酰氨基酚、非那西汀、灭酸酯、甲灭酸、甲氯灭酸酯、甲氯灭酸钠、杂芳基乙酸衍生物、托美丁、酮咯酸、双氯芬酸、丙酸衍生物、布洛芬、萘普生钠、萘普生、非诺洛芬、酮洛芬、氟比洛芬、奥沙普秦；烯醇酸、昔康（苯并噻嗪类）衍生物、吡罗昔康、美洛昔康、替诺昔康、安吡昔康、屈噁昔康、匹伏昔康、吡唑酮衍生物、保泰松、羟布宗、安替比林、氨基比林、安乃近、考昔类药物、塞来考昔、罗非考昔、萘丁美酮、阿扎丙宗、尼美舒利、吲哚美辛、舒林酸、依托度酸、双氟尼酸和异丁基苯基丙酸。所述抗毒蕈碱剂选自奥昔布宁、索非那新、达非那新和阿托品。

[0167] 在一些实施方式中，所述药物组合物包含单一镇痛剂、单一 α－阻滞剂和单一抗毒蕈碱剂。在一些实施方式中，所述药物组合物包含单一镇痛剂、单一 5α－还原酶抑制剂和单一抗毒蕈碱剂。在一个实施方式中，所述单一镇痛剂是阿司匹林。在另一个实施方式中，所述单一镇痛剂是布洛芬。在另一个实施方式中，所述单一镇痛剂是萘普生或萘普生钠。在另一个实施方式中，所述单一镇痛剂是吲哚美辛。在另一个实施方式中，所述单一镇痛剂是萘丁美酮。在另一个实施方式中，所述单一镇痛剂是对乙酰氨基酚。在另一个实施方式中，所述单一 α－阻滞剂是坦洛新。所述镇痛剂、α－阻滞剂、5α－还原酶抑制剂和抗毒蕈碱剂可以以上述范围内的剂量给药。在一些实施方式中，所述药物组合物进一步包含抗利尿剂或解痉剂。

[0168] 在一些实施方式中，所述药物组合物包含一种或多种单独或联合的用量为 50-2000mg, 50-1500mg, 50-1200mg, 50-1000mg, 50-800mg, 50-600mg, 50-500mg, 50-400mg, 50-300mg, 50-250mg, 50-200mg, 50-150mg, 50-100mg, 100-2000mg, 100-1500mg, 100-1200mg, 100-1000mg, 100-800mg, 100-600mg, 100-400mg, 100-250mg, 250-2000mg, 250-1500mg, 250-1200mg, 250-1000mg, 250-800mg, 250-600mg, 250-400mg, 400-2000mg, 400-1500mg, 400-1200mg, 400-1000mg, 400-800mg, 400-600mg, 600-2000mg, 600-1500mg, 600-1200mg, 600-1000mg, 600-800mg, 800-2000mg, 800-1500mg, 800-1200mg, 800-1000mg, 1000-2000mg, 1000-1500mg, 1000-1200mg, 1200-2000mg, 1200-1500mg 或 1500-2000mg 的镇痛剂，其中，所述组合物被配制成具有一种释放曲线的延长释放，在该释放曲线中，所述一种或多种镇痛剂在 5-24 小时、5-8、8-16 小时或 16-24 小时的时段内连续释放。

[0169] 在一些实施方式中，所述组合物被配制成具有一种释放曲线的延长释放，在该释放曲线中，活性成分的至少 90％在 5-24 小时、5-8、8-16 小时或 16-24 小时的时段内连续释放。

[0170] 在一些实施方式中，所述组合物被配制成具有一种释放曲线的延长释放，在该释放曲线中，活性成分在一个 5、6、7、8、10、12、14、16、18、20、22 或 24 小时的时段内连续释放。

[0171] 在另外一些实施方式中，所述组合物被配制成具有一种释放曲线的延长释放，在该释放曲线中，活性成分在 5-24 小时、5-8、8-16 小时或 16-24 小时的时段内以稳定的速率释放。在另外一些实施方式中，所述组合物被配制成具有一种释放曲线的延长释放，在该释放曲线中，活性成分在 5、6、7、8、10、12、14、16、18、20、22 或 24 小时的时段内以稳定的速率释放。此处使用的“在一个时段以稳定的速率”定义为一种释放曲线，在该释放曲线中，在给定时段的任意点的释放速率在该给定时段的平均释放速率的 30％ -300％内。例如，如果 80mg 阿司匹林在一个 8 小时时段内以稳定的速率释放，该时段内的平均速率为 10mg/hr，那么在这个时段任意时间的实际释放速率在 3mg/hr 到 30mg/hr 的范围内（即，8 小时时段之

内的 10mg/hr 平均释放速率的 30％ -300％内)。

[0172] 在一些实施方式中，所述镇痛剂选自阿司匹林、布洛芬、萘普生钠、萘普生、吲哚美辛、萘丁美酮和对乙酰氨基酚。所述药物组合物被配制为提供镇痛剂的小量稳定释放，从而维持血液中有效药物浓度，使得相比于立即释放制剂，单次用药中的药物总量就减少了。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0173] 在一些实施方式中，所述药物组合物包含 50-400mg，50-250mg，250-400mg 或 400-600mg 的被配制为具有一种释放曲线的延长释放的镇痛剂，在该释放曲线中，至少 90％的镇痛剂在 5-8、8-16 小时或 16-24 小时的时段内连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0174] 在一个特定的实施方式中，所述药物组合物包含 50-250mg 的被配制为具有一种释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，至少 90％的对乙酰氨基酚在 5-8、8-16 小时或 16-24 小时的时段内连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0175] 在另外一个特定的实施方式中，所述药物组合物包含 250-400mg 的被配制为具有一种释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，90％的对乙酰氨基酚在 5-8、8-16 小时或 16-24 小时的时段内连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0176] 在另外一个特定的实施方式中，所述药物组合物包含 400-600mg 的被配制为具有一种释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，90％的对乙酰氨基酚在 5-8、8-16 小时或 16-24 小时的时段内连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0177] 在另外一个特定的实施方式中，所述药物组合物包含 600-800mg 的被配制为具有一种释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，90％的对乙酰氨基酚在 5-8、8-16 小时或 16-24 小时的时段内连续地或以一个稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0178] 在另外一个特定的实施方式中，所述药物组合物包含 800-1000mg 的被配制为具有一种释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，至少 90％的对乙酰氨基酚在 5-8、8-16 小时或 16-24 小时的时段内连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0179] 在另外的一些实施方式中，所述药物组合物包含一种或多种单独或联合的用量为 50-2000mg，50-1500mg，50-1200mg，50-1000mg，50-800mg，50-600mg，50-500mg，50-400mg，50-300mg，50-250mg，50-200mg，100-2000mg，100-1500mg，100-1200mg，100-1000mg，100-800mg，100-600mg，100-500mg，100-400mg，100-300mg，100-200mg，200-2000mg，200-1500mg，200-1200mg，200-1000mg，200-800mg，200-600mg，200-400mg，400-2000mg，400-1500mg，400-1200mg，400-1000mg，400-800mg，400-600mg，600-2000mg，600-1500mg，600-1200mg，600-1000mg，600-800mg，800-2000mg，800-1500mg，800-1200mg，800-1000mg，1000-2000mg，1000-1500mg，1000-1200mg，1200-2000mg，1200-1500mg 或 1500-2000mg 的镇痛剂，其中，所述镇痛剂被配制成以一种两段释放曲线为特点的延长释放，在该释放曲线中，镇痛剂的 20-50％在施用 2 小时内释放，而剩余部分在 5-24 小时的时段内连续地或以稳定的速率释放。其他活

性成分可在施用后立即释放或随镇痛剂释放。

[0180] 在另外的一个实施方式中，所述镇痛剂被配制成具有一种两段释放曲线的延长释放，在该释放曲线中，镇痛剂的 20、30、40 或 50％在施用 2 小时内释放，而剩余部分在 5-8、8-16 或 16-24 小时的时段内连续地或以稳定的速率释放。在一个实施方式中，所述镇痛剂选自阿司匹林、布洛芬、萘普生钠、萘普生、吲哚美辛、萘丁美酮和对乙酰氨基酚。在另外的一个实施方式中，所述镇痛剂为对乙酰氨基酚。在一些实施方式中，所述药物组合物进一步包含抗毒蕈碱剂、抗利尿剂或解痉剂。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0181] 在另外的一个实施方式中，所述药物组合物包含 50-400mg 的被配制为具有一种两段释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，对乙酰氨基酚的 20、30、40 或 50％在施用 2 小时内释放，而剩余部分在 5-8、8-16 或 16-24 小时的时段连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0182] 在另外的一个实施方式中，所述药物组合物包含 100-300mg 的被配制为具有一种两段释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，对乙酰氨基酚的 20、30、40 或 50％在施用 2 小时内释放，而剩余部分在 5-8、8-16 或 16-24 小时的时段内连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0183] 在另外的一个实施方式中，所述药物组合物包含 400-600mg 的被配制为具有一种两段释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，对乙酰氨基酚的 20、30、40 或 50％在施用 2 小时内释放，而剩余部分在 5-8、8-16 或 16-24 小时的时段连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0184] 在另外的一个实施方式中，所述药物组合物包含 600-800mg 的被配制为具有一种两段释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，对乙酰氨基酚的 20、30、40 或 50％在施用 2 小时内释放，而剩余部分在 5-8、8-16 或 16-24 小时的时段内连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0185] 在另外的一个实施方式中，所述药物组合物包含 800-1000mg 的被配制为具有一种两段释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，对乙酰氨基酚的 20、30、40 或 50％在施用 2 小时内释放，而剩余部分在 5-8、8-16 或 16-24 小时的时段连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0186] 在另外的一个实施方式中，所述药物组合物包含 1000-1200mg 的被配制为具有一种两段释放曲线的延长释放的对乙酰氨基酚，在该释放曲线中，对乙酰氨基酚的 20、30、40 或 50％在施用 2 小时内释放，而剩余部分在 5-8、8-16 或 16-24 小时的时段内连续地或以稳定的速率释放。其他活性成分可在施用后立即释放或随镇痛剂释放。

[0187] 本申请的另一方面涉及一种通过向需要其的受试者施用 (1) 一种或多种镇痛剂、(2) α－阻滞剂或 5α－还原酶抑制剂或两者的结合，和 (3) 一种或多种抗利尿剂而治疗夜尿症的方法。在某些实施方式中，所述抗利尿剂用于 :(1) 增加血管加压素分泌 ;(2) 增加血管加压素受体激活 ;(3) 减少心房利钠肽 (ANP) 或 C 型利钠肽 (CNP) 的分泌 ;或 (4) 减少 ANP 和 / 或 CNP 受体激活。

[0188] 抗利尿剂的例子包括，但不限于，抗利尿激素 (ADH)、血管紧张素 II、醛固酮、血管加压素、血管加压素类似物 (例如，去氨加压素精氨加压素、赖氨加压素、苯赖加压素、鸟氨加压素、特利加压素) ;血管加压素受体激动剂、心房利钠肽 (ANP) 和 C 型利钠肽 (CNP) 受

体（即 NPR1、NPR2、NPR3）拮抗剂（例如，HS-142-1、靛红、[Asu7,23′]b-ANP-(7-28)]、安南汀、来自天蓝色链霉菌 (Streptomyces coerulescens) 的环肽，以及 3G12 单克隆抗体）；促生长素抑制素 2 型受体拮抗剂（如，促生长素抑制素），及其药学上可接受的衍生物、类似物、盐、水合物和溶剂合物。

[0189] 在某一实施方式中，所述一种或多种镇痛剂、α－阻滞剂和 / 或 5α－还原酶抑制剂被配制成延长释放，而所述一种或多种抗利尿剂被配制成立即释放。在另外一些实施方式中，所述一种或多种镇痛剂、α－阻滞剂和 / 或 5α－还原酶抑制剂被配制成延迟释放，而所述抗利尿剂被配制成立即释放。在一些实施方式中，延迟释放制剂延迟所述活性成分（例如，所述镇痛剂、抗毒蕈碱剂、抗利尿剂和解痉剂）的释放达 1、2、3、4 或 5 小时。

[0190] 本申请的另一个方面涉及一种通过向需要其的人施用包含利尿剂的第一药物组合物，然后施用包含 (1) 一种或多种镇痛剂和 (2) 一种或多种 α－阻滞剂、一种或多种 5α－还原酶抑制剂或两者的结合的第二药物组合物来缓解尿频的方法。第一药物组合物的剂量和配方设置为在施用 6 小时以内具有利尿效果，且其在睡前至少 8 或 7 小时施用。所述第二药物组合物在睡前 2 小时内施用。所述第一药物组合物配制为立即释放，且所述第二药物组合物配制为延长释放，或者延迟的延长释放。

[0191] 利尿剂的例子包括但不限于，酸化盐，如 CaCl2 和 NH4Cl ；精氨酸加压素受体 2 拮抗剂，如两性霉素 B 和枸橼酸锂 ；促水排泄药，如黄花 (Goldenrod) 和杜松 (Junipe) ；Na-H 交换剂拮抗剂，如多巴胺 ；碳酸酐酶抑制剂，如乙酰唑胺和多佐胺 ；髓袢利尿剂，如布美他尼、依他尼酸、呋塞米和托塞米 ；渗压性利尿剂，如葡萄糖和甘露醇 ；保钾利尿剂，如阿米洛利、螺旋内酯固醇、氨苯蝶啶、烯睾丙酸钾 ；噻嗪类，如苄氟噻嗪和氢氯噻嗪 ；以及黄嘌呤，如咖啡因、茶碱和可可碱。

[0192] 在一些实施方式中，所述第二药物组合物进一步包含一种或多种抗毒蕈碱剂。所述抗毒蕈碱剂的例子包括，但不限于奥昔布宁、索非那新、达非那新、非索罗定、托特罗定、曲司氯铵和阿托品。所述第二药物组合物可以配制为立即释放制剂或延迟释放制剂或延长释放制剂。在其他的一些实施方式中，所述第二药物组合物进一步包含一种或多种抗利尿剂。在其他的一些实施方式中，所述第二药物组合物进一步包含一种或多种解痉剂。本申请的另一方面涉及一种通过向需要其的受试者可选择地施用两种或更多种镇痛剂来防止发生耐药性以缓解尿频的方法。在一个实施方式中，该方法包括施用针对第一时段的第一镇痛剂，然后施用针对第二时段的第二镇痛剂。在另一个实施方式中，该方法进一步包括施用针对第三时段的第三镇痛剂。所述第一、第二和第三镇痛剂彼此不同，且其中至少一种被配制为延长释放或延迟的延长释放。在一个实施方式中，所述第一镇痛剂是对乙酰氨基酚，所述第二镇痛剂是布洛芬且所述第三镇痛剂是萘普生钠。各个时段的长短可以根据受试者对的各个镇痛剂的反应有所不同。在一些实施方式中，每个时段持续时间从三天至三周。在另一个实施方式中，第一、第二和第三镇痛剂都被配制为延长释放或延迟的延长释放。

[0193] 本申请的另一方面涉及一种包含多种活性成分和药学上可接受的载体的药物组合物，其中，所述多种活性成分的至少一种被配制为延长释放或延迟的延长释放。在一些实施方式中，所述多种活性成分包含一种或多种镇痛剂和一种或多种抗利尿剂。在另一些实施方式中，所述多种活性成分包含一种或多种镇痛剂、一种或多种 α－阻滞剂、一种或多种 5α－还原酶抑制剂和一种或多种抗毒蕈碱剂。在另一些实施方式中，所述多种活性成分包

含一种或多种镇痛剂、一种或多种 α - 阻滞剂、一种或多种抗利尿剂和一种或多种抗毒蕈碱剂。在另一些实施方式中，所述药物组合物包含两种不同的选自乙酰水杨酸、布洛芬、萘普生钠、萘普生、萘丁美酮、对乙酰氨基酚和吲哚美辛的镇痛剂。在另外一些实施方式中，所述药物组合物包含一种选自乙酰水杨酸、布洛芬、萘普生钠、萘丁美酮、对乙酰氨基酚和吲哚美辛的镇痛剂；一种或多种 α - 阻滞剂以及选自奥昔布宁、索非那新、达非那新和阿托品的抗毒蕈碱剂。

[0194] 在另外一些实施方式中，本申请所述药物组合物进一步包含一种或多种解痉剂和 / 或一种或多种抗利尿剂。解痉剂的例子包括，但不限于，卡立普多、苯（并）二氮卓类、巴氯芬、环苯扎珠、美他沙酮、美索巴莫、可乐定、可乐定类似物和丹曲洛林。在一些实施方式中，解痉剂以每日 1mg 至 1000mg，1mg 至 100mg，10mg 至 1000mg，10mg 至 100mg，20mg 至 1000mg，20mg 至 800mg，20mg 至 500mg，20mg 至 200mg，50mg 至 1000mg，50mg 至 800mg，50mg 至 200mg，100mg 至 800mg，100mg 至 500mg，200mg 至 800mg 和 200mg 至 500mg 的剂量使用。解痉剂可以单独或与药物组合物中其他活性成分一起被配制成立即释放、延长释放、延迟 - 延长释放或其组合。

[0195] 在一些实施方式中，所述药物组合物包含一种或多种选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚的总量为 50-400mg 每剂的镇痛剂，一种或多种 α - 阻滞剂以及一种或多种选自奥昔布宁、索非那新、达非那新和阿托品的总量为 1-25mg 的抗毒蕈碱剂，其中，所述药物组合物被配制成具有一种两阶段释放曲线的延长释放，在该释放曲线中，活性成分的 20-60％在施用 2 小时内被释放，而活性成分的剩余部分在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或者保持稳定速率地释放。

[0196] 在一些实施方式中，所述药物组合物包含一种或多种选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚的总量为 50-400mg 每剂的镇痛剂，一种或多种 α - 阻滞剂以及一种或多种抗利尿剂，所述抗利尿剂选自抗利尿激素 (ADH)、血管紧张素 II、醛固酮、血管加压素、血管加压素类似物（例如，去氨加压素精氨加压素、赖氨加压素、苯赖加压素、鸟氨加压素、特利加压素）；血管加压素受体激动剂、心房利钠肽 (ANP) 和 C 型利钠肽 (CNP) 受体（即 NPR1、NPR2、NPR3）拮抗剂（例如，HS-142-1、靛红、[Asu7,23’] b-ANP-(7-28)]、安南汀 (anantin)、来自天蓝色链霉菌 (Streptomyces coerulescens) 的环肽，以及 3G12 单克隆抗体）；促生长素抑制素 2 型受体拮抗剂（如，促生长素抑制素），及其药学上可接受的衍生物、类似物、盐、水合物和溶剂合物，其中，所述药物组合物被配制成具有一种两阶段释放曲线的延长释放，在该释放曲线中，活性成分的 20-60％在施用 2 小时内被释放，而剩余部分在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或者保持稳定速率地释放。

[0197] 在一些实施方式中，所述药物组合物包含 (1) 一种或多种选自阿司匹林、布洛芬、萘普生、萘普生钠、吲哚美辛、萘丁美酮和对乙酰氨基酚的用量为 50-400mg 每剂的镇痛剂，(2) 一种或多种 α - 阻滞剂，或一种或多种 5α - 还原酶抑制剂或其二者，和 (3) 一种或多种选自卡立普多、苯（并）二氮卓类、巴氯芬、环苯扎珠、美他沙酮、美索巴莫、可乐定、可乐定类似物和丹曲洛林的总量为 50-500mg 的解痉剂，其中，所述药物组合物被配制成具有一种两阶段释放曲线的延长释放，在该释放曲线中，活性成分的 20-60％在施用 2 小时内被释

放，而剩余部分在 5-24 小时、5-8 小时、8-16 小时或 16-24 小时的时段内被连续地或者保持稳定速率地释放。

[0198] 在此使用的“药学上可接受的载体”包括所有的和任意的溶剂、分散介质、包衣、抗细菌和抗真菌剂、等渗和吸收延缓剂、甜味剂等。所述药学上可接受的载体可由较宽范围的材料制备，所述材料包括，但不限于，调味剂、甜味剂和混杂材料，如为了制备特别的治疗组合物所需的缓冲剂和吸收剂。这种与药学活性物质一起使用的介质和试剂的用途在本领域中是公知的。除了与活性成分不相容的常规介质或试剂以外，其他所包括的物质在治疗组合物中的应用都在考虑范围内。

[0199] 本发明将通过以下的非限制性实施例进一步说明。在本申请中引用的所有参考文件、专利和公开的专利申请的内容都通过引用方式并入本申请。

[0200] 实施例 1 :排尿冲动的抑制

[0201] 招收男女都参加的 20 名志愿受试者，他们各自都经历了过早的排尿冲动或排尿需求，这干扰了他们足以感到充分休息的一段时间的睡眠的能力。每个受试者在就寝前以单剂量摄入 400 至 800mg 的布洛芬。至少有 14 个受试者报告说，因为没有被频繁的排尿冲动唤醒，他们能够更好地休息。

[0202] 有几名受试者报告说，在夜间使用布洛芬几个星期以后，不再能实现排尿冲动不频繁的裨益。然而，所有这些受试者都进一步报告说，在放弃服用药剂几天以后，又获得了这样的裨益。

[0203] 实施例 2 :镇痛剂、肉毒杆菌神经毒素和抗毒蕈碱剂对巨噬细胞对炎症和非炎症性刺激的反应的影响

[0204] 实验设计

[0205] 本研究旨在确定镇痛剂和抗毒蕈碱剂在控制对由 COX2 和前列腺素 (PGE、PGH 等) 介导的炎症和非炎症性刺激的巨噬细胞反应中的剂量和体外效力。它建立了对膀胱细胞中炎症和非炎症性效应物的基线 (剂量和动力学) 的反应。简言之，在不存在或存在各种效应物的情况下，使培养细胞暴露于镇痛剂和 / 或抗毒蕈碱剂。

[0206] 所述效应物包括 :脂多糖 (LPS)、发炎剂和 Cox2 诱导物，作为炎症性刺激物 ;卡巴胆碱或乙酰胆碱、平滑肌收缩刺激剂，作为非炎症性刺激物 ;肉毒杆菌神经毒素 A，一种已知的乙酰胆碱释放的抑制剂，作为阳性对照 ;花生四烯酸 (AA)，伽玛亚麻酸 (DGLA) 或二十碳五烯酸 (EPA)，作为前列腺素的前体，他们是在通过环氧合酶 (COX1 和 COX-2) 和终端前列腺素合酶在细胞内依次氧化 AA、DGLA 或 EPA 之后而产生的。

[0207] 所述镇痛剂包括 :水杨酸盐，如阿司匹林、异丁基丙酸酚酸衍生物 (布洛芬) 如雅维 (Advil)、布洛芬制剂 (Motrin)、磺胺二甲噁唑 (Nuprin) 和 Medipren ;萘普生钠，如萘普生钠 (Aleve)、萘普生制剂 (Anaprox)、Antalgin、Feminax Ultra、萘普生 (Flanax)、Inza、Midol Extended Relief、Nalgesin、Naposin、萘普生缓释片剂 (Naprelan)、Naprogesic、萘普生 (Naprosyn)、萘普生 (Naprosyn) 混悬液、EC- 萘普生 (EC-Naprosyn)、Narocin、萘普生 (Proxen)、Synflex 和 Xenobid ;醋酸衍生物，如吲哚美辛 (Indocin) ;1- 萘乙酸衍生物，如萘丁美酮或瑞力芬 ;N- 乙酰基对氨基苯酚 (APAP) 衍生物，如对乙酰氨基酚或扑热息痛 (泰诺林) 和塞来考昔。

[0208] 所述抗毒蕈碱剂包括 :奥昔布宁、索非那新、达非那新和阿托品。

[0209] 使巨噬细胞受到以下物质的短期(1-2 小时)或长期(24-48 小时)刺激:

[0210] (1) 不同剂量的每种单独的镇痛剂。

[0211] (2) 在 LPS 存在的情况下不同剂量的每种镇痛剂。

[0212] (3) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种镇痛剂。

[0213] (4) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种镇痛剂。

[0214] (5) 不同剂量的单独的肉毒杆菌神经毒素 A。

[0215] (6) 在 LPS 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0216] (7) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0217] (8) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0218] (9) 不同剂量的单独的每种抗毒蕈碱剂。

[0219] (10) 在 LPS 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0220] (11) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种抗毒蕈碱剂。

[0221] (12) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0222] 然后分析细胞的 PGH_2、PGE、PGE_2、前列腺环素、血栓烷、IL-1β、IL-6、TNF-α 的释放,COX2 活性,cAMP 和 cGMP 的产生,IL-1β、IL-6、TNF-α 和 COX2mRNA 的产生,以及 CD80、CD86 和 MHC II 类分子的表面表达。

[0223] 材料和方法

[0224] 巨噬细胞

[0225] 在此研究中使用鼠科 RAW264.7 或 J774 巨噬细胞(由 ATCC 获得)。将细胞保持在含有 RPMI 1640 的培养基中,并补充有 10%胎牛血清 (FBS)、15mM HEPES、2mM 左旋谷酰胺、100U/ml 青霉素和 100μg/ml 的链霉素。将细胞在 37℃,5%的 CO_2 气氛下培养,且每星期分离(传代)一次。

[0226] 巨噬细胞以镇痛剂的体外治疗

[0227] 将 RAW264.7 巨噬细胞以 $1.5x10^5$ 个细胞/孔(在 100μl 培养基中)的细胞密度接种在 96 孔板中。将细胞用以下物质处理:(1) 不同浓度的镇痛剂(对乙酰氨基酚、阿司匹林、布洛芬或萘普生),(2) 不同浓度的脂多糖 (LPS),它是对巨噬细胞的炎症性刺激的效应物,(3) 不同浓度的卡巴胆碱或乙酰胆碱,它们是非炎症性刺激的效应物,(4) 镇痛剂和 LPS 或 (5) 镇痛剂和卡巴胆碱或乙酰胆碱。简言之,将镇痛剂溶解在无 FBS 的培养基中(即,补充有 15mM HEPES、2mM 左旋谷酰胺、100U/ml 青霉素和 100μg/ml 的链霉素的 RPMI 1640),并通过用相同介质的连续稀释稀释到所需浓度。对于在没有 LPS 存在的情况下以镇痛剂处理的细胞,向每个孔中加入 50μl 的镇痛剂溶液和 50μl 的无 FBS 的培养基。对于在有 LPS 存在的情况下以镇痛剂处理的细胞,向每个孔中加入 50μl 的镇痛剂溶液和 50μl 的在无 FBS 的培养基中的 LPS(来自鼠伤寒沙门氏菌 (Salmonella typhimurium))。所有的条件重复测试两次。

[0228] 在培养 24 或 48 小时后,收集 150μl 的培养上清液,在 4℃,8,000rpm 下旋转 2 分钟以除去细胞和碎片,并在 -70℃储存以用于通过 ELISA 分析细胞因子的反应。通过在 500μl 的磷酸盐缓冲液 (PBS) 中离心(在 4℃,1,500rpm 下 5 分钟)收集和洗涤细胞。然后将一半的细胞在液氮中快速冻结,并在 -70℃下储存。将剩余的细胞用荧光单克隆抗体染色并通过流式细胞计分析。

[0229] 辅刺激分子表达的流式细胞计分析

[0230] 对于流式细胞计分析，将巨噬细胞在 100μl 的 FACS 缓冲液（具有 2％的牛血清白蛋白 (BSA) 和 0.01％ NaN3 的磷酸盐缓冲液 (PBS)）中稀释，并通过添加 FITC- 结合的抗 CD40、PE- 结合的抗 CD80、PE- 结合的抗 -CD86 抗体、抗 MHC II 类 ($I\text{-}A^d$)PE(BD 生物科学）而在 4℃下染色 30 分钟。然后将细胞通过在 300μl 的 FACS 缓冲液中离心（在 4℃，1,500rpm 下 5 分钟）清洗。在第二次洗涤后，细胞重新悬浮在 200μl 的 FACS 缓冲液中，且借助 Accuri C6 流式细胞计 (BD 生物科学）分析表达给定标记（单阳性）或者标记的组合（双阳性）的细胞的百分比。

[0231] 通过 ELISA 分析细胞因子的反应

[0232] 对培养上清液进行细胞因子特异性 ELISA，以确定在用镇痛剂、LPS 单独处理或者 LPS 和镇痛剂结合处理的巨噬细胞的培养物中的 IL-1β，IL-6 和 TNF-α 反应。这些测定是在用在 0.1M 的碳酸氢钠缓冲液 (pH9.5) 中的 100μl 的抗小鼠 IL-6、TNF-α mAbs(BD 生物科学）或 IL-1β mAb(R&D 系统）包被过夜的 Nunc MaxiSorp Immunoplates(Nunc) 上进行的。在用 PBS（每孔 200μl）清洗两次以后，向每个孔（区）中添加 200μl 的 PBS 3％ BSA，且在室温下孵育板 2 小时。通过每孔添加 200μl，再次清洗板两次，重复添加 100μl 的细胞因子标准品和连续稀释的培养上清液，并将该板在 4℃下孵育过夜。最后，将该板清洗两次，并用 100μl 生物素化的抗鼠 IL-6、TNFα mAbs(BD 生物科学）或 IL-1β (R&D 系统）的二抗，随后用过氧化物酶标记的羊抗生物素 mAb(Vector 实验室）孵育。通过添加 2,2′ -连氮 - 双 (3- 乙基苄基噻唑啉 -6- 磺酸）(ABTS) 底物和 H_2O_2(Sigma) 而使比色反应显影，且吸光度使用 Victor® V 多标记微孔板检测仪 (PerkinElmer) 在 415nm 处测量。

[0233] COX2 的活性测定和 cAMP 和 cGMP 的生成

[0234] 在培养的巨噬细胞中的 COX2 的活性通过顺序竞争 ELISA(R&D 系统）确定。cAMP 和 cGMP 的生成通过 cAMP 测定和 cGMP 测定来确定。这些测定在本领域中是通常进行的。

[0235] 结果

[0236] 表 1 总结了由 Raw 264 巨噬细胞株进行的实验以及在镇痛剂对辅刺激分子 CD40 和 CD80 的细胞表面表达的影响方面的主要发现。这些分子的表达是通过 COX2 和炎症信号来刺激的，且因此评估这些分子的表达以确定 COX2 的抑制的功能后果。

[0237] 如表 2 所示，除了最高剂量（即，$5x10^6$nM)（其表现出增强，而不是抑制辅刺激分子的表达）以外，对乙酰氨基酚、阿司匹林、布洛芬和萘普生在所有的测试剂量（即，$5x10^5$nM、$5x10^4$nM、$5x10^3$nM、$5x10^2$nM、50nM 和 5nM) 下抑制巨噬细胞的辅刺激分子 CD40 和 CD80 的基础表达。如图 1A 和 1B 所示，镇痛剂剂量在低至 0.05nM（即，0.00005μM) 时观察到对 CD40 和 CD50 表达的这样的抑制效果。这一发现支持了这样的观点：小剂量的镇痛剂的控制释放比大剂量的急性递送更优选。实验还表明，对乙酰氨基酚、阿司匹林、布洛芬和萘普生对 LPS 诱导的 CD40 和 CD80 的表达具有类似的抑制效果。

[0238] 表 1. 实验总结

[0239]

	对照	LPS 鼠伤寒沙门氏菌	对乙酰氨基酚	阿司匹林	布洛芬	萘普生
实验						
1	X					
2	X	剂量反应（0、5、50、1000）ng/mL				
3	X		剂量反应（0、5、50、500、$5x10^3$、$5x10^4$、$5x10^5$、$5x10^6$）nM			
4	X	X（5 ng/mL） X（50 ng/mL） X（1000 ng/mL）	剂量反应（0、5、50、500、$5x10^3$、$5x10^4$、$5x10^5$、$5x10^6$）nM			
分析						
a	活化/刺激状态的表征：CD40、CD80、CD86 和 MHC II 类的流式细胞计分析					
b	炎症反应的介质：IL-1β、IL-6、TNF-α 的 ELISA 分析					

[0240] 表 2. 主要发现的总结

[0241]

效应物	%阳性	阴性	LPS	镇痛剂剂量（nM）

[0242]

		对照	5ng/mL							
				5x 10^6	5x 10^5	5x 10^4	5x 10^3	500	50	5
	$CD40^+$ $CD80^+$	20.6	77.8							
对乙酰氨基酚	$CD40^+$ $CD80^+$			63	18	12	9.8	8.3	9.5	7.5
阿司匹林	$CD40^+$ $CD80^+$			44	11	10.3	8.3	8	10.5	7.5
布洛芬	$CD40^+$ $CD80^+$			ND*	6.4	7.7	7.9	6.0	4.9	5.8
萘普生	$CD40^+$ $CD80^+$			37	9.6	7.7	6.9	7.2	6.8	5.2
				镇痛剂加 LPS						
对乙酰氨基酚	$CD40^+$ $CD80^+$			95.1	82.7	72.4	68.8	66.8	66.2	62.1
阿司匹林	$CD40^+$ $CD80^+$			84.5	80	78.7	74.7	75.8	70.1	65.7
布洛芬	$CD40^+$ $CD80^+$			ND	67	77.9	72.9	71.1	63.7	60.3
萘普生	$CD40^+$ $CD80^+$			66.0	74.1	77.1	71.0	68.8	72	73

[0243] *ND：未进行（毒性）

[0244] 表 3 总结了几项研究的结果，这些研究测量了成人在口服治疗剂量后的镇痛剂的血清水平。如表 3 中所示，在口服治疗剂量后镇痛剂的最大血清水平在 10^4 至 10^5nM 范围内。因此，在表 2 中的体外测试的镇痛剂剂量覆盖了人体内可实现的浓度范围。

[0245] 表 3. 口服治疗剂量后人血液中的镇痛剂的血清水平

[0246]

镇痛剂药物	分子量	口服治疗剂量后最大血清水平		参考文献
		mg/L	nM	
对乙酰氨基酚（泰诺林）	151.16	11-18	$7.2x10^4$-$1.19x10^5$	*BMC Clinical Pharmacology.2010, 10:10 * Anaesth Intensive Care. 2011, 39:242
阿司匹林（乙酰水杨酸）	181.66	30-100	$1.65x10^5$-$5.5x10^5$	* *Disposition of Toxic Drugs and Chemicals in Man*, 8th Edition, Biomedical Public, Foster City, CA, 2008, pp. 22-25 * J Lab Clin Med. 1984 Jun;103:869
布洛芬（雅维，Motrin）	206.29	24-32	$1.16x10^5$-$1.55x10^5$	* BMC Clinical Pharmacology2010, 10:10 * J Clin Pharmacol. 2001 , 41:330
萘普生（Aleve）	230.26	高 至 60	高至 $2.6x10^5$	* J Clin Pharmacol. 2001 , 41:330

[0247] 实施例 3：镇痛剂、肉毒杆菌神经毒素和抗毒蕈碱剂对小鼠膀胱平滑肌细胞对炎症和非炎症性刺激的反应的影响

[0248] 实验设计

[0249] 本研究旨在说明在实施例 2 中确定的镇痛剂的最优剂量如何影响在细胞培养或组织培养中的膀胱平滑肌细胞，并论述不同类的镇痛剂是否能够协同以更有效地抑制 COX2 和 PGE2 反应。

[0250] 在实施例 2 中描述了效应物、镇痛剂和抗毒蕈碱剂。

[0251] 使小鼠膀胱平滑肌细胞的原代培养物受到以下物质的短期（1-2 小时）或长期（24-48 小时）刺激：

[0252] (1) 不同剂量的每种单独的镇痛剂。

[0253] (2) 在 LPS 存在的情况下不同剂量的每种镇痛剂。

[0254] (3) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种镇痛剂。

[0255] (4) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种镇痛剂。

[0256] (5) 不同剂量的单独的肉毒杆菌神经毒素 A。

[0257] (6) 在 LPS 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0258] (7) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0259] (8) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0260] (9) 不同剂量的单独的每种抗毒蕈碱剂。

[0261] (10) 在 LPS 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0262] (11) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种抗毒蕈碱剂。

[0263] (12) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0264] 然后分析细胞的 PGH_2、PGE、PGE_2、前列腺环素、血栓烷、IL-1β、IL-6、TNF-α 的释放，COX2 活性，cAMP 和 cGMP 的产生，IL-1β、IL-6、TNF-α 和 COX2mRNA 的产生，以及 CD80、CD86 和 MHC II 类分子的表面表达。

[0265] 材料和方法

[0266] 小鼠膀胱细胞的分离和纯化

[0267] 从被安乐死的动物 C57BL/6 小鼠 (8-12 周龄) 取出膀胱细胞，且将细胞通过酶消化分离，随后用 Percoll 梯度纯化。简言之，将从 10 只小鼠得到的膀胱用剪刀切碎为在 10ml 的消化缓冲液 (RPMI 1640、2％胎牛血清、0.5mg/ml 胶原酶、30μg/ml 的 DNA 酶) 中的精制浆液。将膀胱浆液在 37℃下酶消化 30 分钟。将未消化的碎片通过细胞训练器 (cell-trainer) 进一步分散。使细胞混悬液沉淀，并加入到不连续的 20％、40％和 75％ Percoll 梯度以纯化单核细胞。每个实验使用 50-60 个膀胱。

[0268] 在用 RPMI 1640 清洗后，将膀胱细胞再悬浮到补充有 10％胎牛血清、15mM HEPES、2mM 左旋谷酰胺、100U/ml 青霉素和 100μg/ml 的链霉素的 RPMI 1640 中，并以 $3x10^4$ 个细胞/孔 (100μl) 的细胞密度接种到澄清底部的黑色 96 孔细胞培养微培养平板中。将细胞在 37℃，5％的 CO_2 气氛下培养。

[0269] 细胞以镇痛剂的体外治疗

[0270] 将膀胱细胞用镇痛剂溶液 (50μl/孔) 单独或者与卡巴胆碱 (10 摩尔，50μl/孔) (作为非炎症性刺激物的例子) 共同处理，或者与鼠伤寒沙门氏菌的脂多糖 (LPS)(1μg/ml，50μl/孔)(作为非炎症性刺激物的例子) 共同处理。当没有其他的效应物加入细胞中时，向孔中加入 50μl 的无胎牛血清的 RPMI 1640 以调整最终体积为 200μl。

[0271] 在培养 24 小时后，收集 150μl 的培养上清液，在 4℃，8,000rpm 下旋转 2 分钟以除去细胞和碎片，并在 -70℃储存以用于通过 ELISA 分析前列腺素 E2(PGE_2) 的反应。将细胞固定、透化并封闭以使用荧光底物检测环氧合酶 -2(COX-2)。在选定的实验中，细胞在体外刺激 12 小时以用于 COX2 反应的分析。

[0272] COX2 反应分析

[0273] COX2 反应通过使用人/小鼠总 COX2 免疫测定法 (R&D 系统) 的基于细胞的 ELISA 分析，所述分析根据制造商的说明书进行。简言之，在细胞固定和透化以后，向澄清底部的黑色96孔细胞培养微培养平板的孔中加入小鼠抗总COX2和兔抗总GAPDH。经过培育和清洗后，向孔中加入 HRP 结合的抗小鼠 IgG 和 AP 结合的抗兔 IgG。在另一个培育和清洗后，加入 HRP- 荧光底物和 AP- 荧光底物。最后，使用 Victor® V 多标记微孔板检测仪 (PerkinElmer) 读取在 600nm(COX2 荧光) 和 450nm(GAPDH 荧光) 处发出的荧光。结果表示为总 COX2 的相对水平，其通过相对荧光单位 (RFUs) 确定，并标准化为管家蛋白 GAPDH。

[0274] PGE2 反应分析

[0275] 前列腺素 E2 的反应通过顺序竞争 ELISA(R&D 系统) 分析。具体而言，向由山羊抗小鼠多克隆抗体包覆的 96 孔聚苯乙烯微孔板的孔中加入培养上清液或 PGE2 标准样。在微孔板振荡器上孵育一小时后，加入 HRP 结合的 PGE2，并将板在室温下额外孵育两小时。然后

清洗板，并向每个孔中加入 HRP 底物溶液。容许显色 30 分钟，并通过在 450nm（在 570nm 处校正波长）处读取板之前加入硫酸以停止反应。结果表示为 PGE2 平均 pg/ml。

[0276] 其他实验

[0277] PGH2、PGE、前列腺环素 (Prostacydin)、血栓烷、IL-1β、IL-6 和 TNF-α 的释放，cAMP 和 cGMP 的产生，IL-1β、IL-6、TNF-α 和 COX2mRNA 的产生，以及 CD80、CD86 和 MHC II 类分子的表面表达采用如实施例 2 中所述的方法确定。

[0278] 镇痛剂抑制小鼠膀胱细胞对炎症性刺激的 COX2 反应

[0279] 对几种镇痛剂（对乙酰氨基酚、阿司匹林、布洛芬和萘普生）在 5μM 或 50μM 的浓度下对小鼠膀胱细胞进行测试，以确定镇痛剂是否能诱发 COX2 反应。24 小时培养的分析表明，所测试的镇痛剂均未诱导在体外小鼠膀胱细胞中的 COX2 反应。

[0280] 还测试了这些镇痛剂对体外的小鼠膀胱细胞对卡巴胆碱或 LPS 刺激的 COX2 反应的影响。如表 1 所示，测试的卡巴胆碱的剂量对于小鼠膀胱细胞中的 COX-2 水平没有显著影响。另一方面，LPS 显著增加总 COX2 水平。值得注意的是，对乙酰氨基酚、阿司匹林、布洛芬和萘普生均能抑制 LPS 对 COX2 水平的影响。当这些药物在 5μM 或 50μM 测试时，可以看出镇痛剂的抑制效果（表 4）。

[0281] 表 4. 在体外刺激和镇痛剂处理后小鼠膀胱细胞的 COX2 表达

[0282]

刺激物	镇痛剂	总 COX2 水平（标准化的 RFUs）
无	无	158±18
卡巴胆碱（mM）	无	149±21
LPS（1μg/ml）	无	420±26
LPS（1μg/ml）	对乙酰氨基酚（5μM）	275±12
LPS（1μg/ml）	阿司匹林（5μM）	240±17
LPS（1μg/ml）	布洛芬（5μM）	253±32
LPS（1μg/ml）	萘普生（5μM）	284±11
LPS（1μg/ml）	对乙酰氨基酚（50μM）	243±15
LPS（1μg/ml）	阿司匹林（50μM）	258±21
LPS（1μg/ml）	布洛芬（50μM）	266±19
LPS（1μg/ml）	萘普生（50μM）	279±23

[0283] 镇痛剂抑制小鼠膀胱细胞对炎症性刺激的 PGE2 反应

[0284] 测量在小鼠膀胱细胞培养上清液中的 PGE2 的分泌，以确定因镇痛剂的小鼠膀胱细胞 COX2 水平改变的生物学意义。如表 5 所示，在未刺激的膀胱细胞或在卡巴胆碱的存在下培养的膀胱细胞的培养上清液中未检测到 PGE2。与上述的 COX2 反应相一致的，用 LPS 刺激小鼠膀胱细胞诱导 PGE2 的高水平分泌。镇痛剂对乙酰氨基酚、阿司匹林、布洛芬和萘普

生的添加抑制了 LPS 对 PGE2 分泌的影响，且在用 5 或 50μM 剂量的镇痛剂处理的细胞反应之间并未观察到区别。

[0285] 表 5. 在体外刺激和镇痛剂处理后小鼠膀胱细胞的 PGE2 分泌

[0286]

刺激物	镇痛剂	PGE2 水平（pg/ml）
无	无	＜20.5
卡巴胆碱（mM）	无	＜20.5
LPS（1μg/ml）	无	925±55
LPS（1μg/ml）	对乙酰氨基酚（5μM）	619±32
LPS（1μg/ml）	阿司匹林（5μM）	588±21
LPS（1μg/ml）	布洛芬（5μM）	593±46
LPS（1μg/ml）	萘普生（5μM）	597±19
LPS（1μg/ml）	对乙酰氨基酚（50μM）	600±45
LPS（1μg/ml）	阿司匹林（50μM）	571±53
LPS（1μg/ml）	布洛芬（50μM）	568±32
LPS（1μg/ml）	萘普生（50μM）	588±37

[0287] 总之，这些数据表明仅用镇痛剂在 5μM 或 50μM 下不会诱导小鼠膀胱细胞中的 COX2 和 PGE2 反应。然而，在 5μM 或 50μM 下，镇痛剂显著抑制体外由 LPS(1μg/ml) 刺激的小鼠膀胱细胞的 COX2 和 PGE2 反应。未观察到镇痛剂对由卡巴胆碱 (1mM) 刺激的小鼠膀胱细胞的 COX2 和 PGE2 反应的显著影响。

[0288] 实施例 4：镇痛剂、肉毒杆菌神经毒素和抗毒蕈碱剂对小鼠膀胱平滑肌细胞收缩的影响

[0289] 实验设计

[0290] 使培养的小鼠或大鼠膀胱平滑肌细胞和小鼠或大鼠的膀胱平滑肌组织在不同浓度的镇痛剂和 / 或抗毒蕈碱剂的存在下暴露于炎症性刺激物和非炎症性刺激物。测量刺激诱导的肌肉收缩以评估镇痛剂和 / 或抗毒蕈碱剂的抑制效果。

[0291] 在实施例 2 中描述了效应物、镇痛剂和抗毒蕈碱剂。

[0292] 使小鼠膀胱平滑肌细胞的原代培养物受到以下物质的短期 (1-2 小时) 或长期 (24-48 小时) 刺激 ：

[0293] (1) 不同剂量的每种单独的镇痛剂。

[0294] (2) 在 LPS 存在的情况下不同剂量的每种镇痛剂。

[0295] (3) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种镇痛剂。

[0296] (4) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种镇痛剂。

[0297] (5) 不同剂量的单独的肉毒杆菌神经毒素 A。

[0298] (6) 在 LPS 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0299] (7) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0300] (8) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0301] (9) 不同剂量的单独的每种抗毒蕈碱剂。

[0302] (10) 在 LPS 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0303] (11) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种抗毒蕈碱剂。

[0304] (12) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0305] 材料和方法

[0306] 如实施例 3 所述分离原代小鼠膀胱细胞。在选定的实验中，使用膀胱组织的培养物。使用 Grass 多道记录仪（美国 Quincy Mass）记录膀胱平滑肌细胞收缩。

[0307] 实施例 5：口服镇痛剂和抗毒蕈碱剂对小鼠膀胱平滑肌细胞的 COX2 和 PGE2 反应的影响。

[0308] 实验设计

[0309] 对正常小鼠和患有膀胱过度活跃综合征的小鼠给予口服剂量的阿司匹林、萘普生钠、布洛芬、吲哚美辛、萘丁美酮、泰诺林、塞来考昔、奥昔布宁、索非那新、达非那新、阿托品及其组合。对照组包括未处理的正常小鼠和未处理的患有膀胱过度活跃综合征的 OAB 小鼠。最后剂量 30 分钟后，收集膀胱并用卡巴胆碱或乙酰胆碱离体刺激。在选定的实验中，膀胱在用卡巴胆碱刺激之前用肉毒杆菌神经毒素 A 处理。将动物保留在代谢笼中，并评估排尿频率（和体积）。通过监测水摄取和笼窝重 (cage litter weight) 确定膀胱排出量。通过 ELISA 测定血清 PGH_2、PGE、PGE_2、前列腺环素、血栓烷、IL-1β、IL-6、TNF-α、cAMP 和 cGMP 水平。在全血细胞中的 CD80、CD86、MHC II 类的表达通过流式细胞计检测。

[0310] 在实验结束后，将动物安乐处死并用 Grass 多道记录仪记录离体膀胱收缩。将膀胱部分固定在福尔马林中，且通过免疫组织化学分析 COX2 反应。

[0311] 实施例 6：镇痛剂、肉毒杆菌神经毒素和抗毒蕈碱剂对人膀胱平滑肌细胞对炎症和非炎症性刺激的反应的影响

[0312] 实验设计

[0313] 设计本研究以表征在实施例 1 至 5 中确定的镇痛剂的最优剂量如何影响在细胞培养或组织培养中的人膀胱平滑肌细胞，并论述不同类的镇痛剂是否能够协同以更有效地抑制 COX2 和 PGE2 反应。

[0314] 在实施例 2 中描述了效应物、镇痛剂和抗毒蕈碱剂。

[0315] 使人膀胱平滑肌细胞受到以下物质的短期 (1-2 小时）或长期 (24-48 小时）刺激：

[0316] (1) 不同剂量的每种单独的镇痛剂。

[0317] (2) 在 LPS 存在的情况下不同剂量的每种镇痛剂。

[0318] (3) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种镇痛剂。

[0319] (4) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种镇痛剂。

[0320] (5) 不同剂量的单独的肉毒杆菌神经毒素 A。

[0321] (6) 在 LPS 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0322] (7) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0323] (8) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0324] (9) 不同剂量的单独的每种抗毒蕈碱剂。

[0325] (10) 在 LPS 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0326] (11) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种抗毒蕈碱剂。

[0327] (12) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0328] 然后分析细胞的 PGH_2、PGE、PGE_2、前列腺环素、血栓烷、IL-1β、IL-6、TNF-α 的释放，COX2 活性，cAMP 和 cGMP 的产生，IL-1β、IL-6、TNF-α 和 COX2mRNA 的产生，以及 CD80、CD86 和 MHC II 类分子的表面表达。

[0329] 实施例 7：镇痛剂、肉毒杆菌神经毒素和抗毒蕈碱剂对人膀胱平滑肌细胞收缩的影响

[0330] 实验设计

[0331] 使培养的人膀胱平滑肌细胞在不同浓度的镇痛剂和 / 或抗毒蕈碱剂的存在下暴露于炎症性刺激物和非炎症性刺激物。测量刺激诱导的肌肉收缩以评估镇痛剂和 / 或抗毒蕈碱剂的抑制效果。

[0332] 在实施例 2 中描述了效应物、镇痛剂和抗毒蕈碱剂。

[0333] 使人膀胱平滑肌细胞受到以下物质的短期 (1-2 小时) 或长期 (24-48 小时) 刺激：

[0334] (1) 不同剂量的每种单独的镇痛剂。

[0335] (2) 在 LPS 存在的情况下不同剂量的每种镇痛剂。

[0336] (3) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种镇痛剂。

[0337] (4) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种镇痛剂。

[0338] (5) 不同剂量的单独的肉毒杆菌神经毒素 A。

[0339] (6) 在 LPS 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0340] (7) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0341] (8) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的肉毒杆菌神经毒素 A。

[0342] (9) 不同剂量的单独的每种抗毒蕈碱剂。

[0343] (10) 在 LPS 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0344] (11) 在卡巴胆碱或乙酰胆碱存在的情况下不同剂量的每种抗毒蕈碱剂。

[0345] (12) 在 AA、DGLA 或 EPA 存在的情况下不同剂量的每种抗毒蕈碱剂。

[0346] 使用 Grass 多道记录仪 (美国 Quincy Mass) 记录膀胱平滑肌细胞收缩。

[0347] 实施例 8：镇痛剂对正常人膀胱平滑肌细胞对炎症和非炎症性信号的反应的影响

[0348] 实验设计：

[0349] 正常的人膀胱平滑肌细胞的培养

[0350] 将正常的人膀胱平滑肌细胞通过酶消化从人膀胱的宏观正常部分分离。将细胞在体外通过在 37℃下在 5％ CO_2 的气氛中在补充有 10％胎牛血清、15mM HEPES、2mM 左旋谷酰胺、100U/ml 青霉素和 100mg/ml 的链霉素的 RPMI 1640 中培养而扩大，并通过用胰蛋白酶处理以分离细胞随后在新的培养瓶中再接种而每星期传代一次。培养的第一星期，培养基补充有 0.5ng/ml 表皮生长因子、2ng/ml 成纤维细胞生长因子和 5μg/ml 胰岛素。

[0351] 体外以镇痛剂处理正常的人膀胱平滑肌细胞

[0352] 将受胰蛋白酶消化的，并以 $3x10^4$ 个细胞 / 孔 (100μl) 的细胞密度接种在微培

养平板中的膀胱平滑肌细胞用镇痛剂溶液(50μl/孔)单独或者与卡巴胆碱(10摩尔,50μl/孔)(作为非炎症性刺激物的例子)共同处理,或者与鼠伤寒沙门氏菌的脂多糖(LPS)(1μg/ml,50μl/孔)(作为非炎症性刺激物的例子)共同处理。当没有其他的效应物加入细胞中时,向孔中加入50μl的无胎牛血清的RPMI 1640以调整最终体积为200μl。

[0353] 在培养24小时后,收集150μl的培养上清液,在4℃,8,000rpm下旋转2分钟以除去细胞和碎片,并在-70℃储存以用于通过ELISA分析前列腺素E2(PGE_2)的反应。将细胞固定、透化并封闭以使用荧光底物检测COX2。在选定的实验中,细胞在体外刺激12小时以用于COX2、PGE2和细胞因子反应的分析。

[0354] COX2、PGE2和细胞因子反应分析

[0355] 如在实施例3中所述,分析COX2和PGE2反应。如在实施例2中所述,分析细胞因子反应。

[0356] 结果

[0357] 镇痛剂抑制正常的人膀胱平滑肌细胞对炎症性和非炎症性刺激物的COX2反应-在培养24小时以后的细胞和培养上清液的分析表明,无单独测试的镇痛剂诱导正常的人膀胱平滑肌细胞中的COX2反应。然而,如表6所总结的,在正常的人膀胱平滑肌细胞中,卡巴胆碱诱导低的但显著的COX2反应。另一方面,LPS处理导致在正常的人膀胱平滑肌细胞中较高水平的COX2反应。对乙酰氨基酚、阿司匹林、布洛芬和萘普生均能抑制卡巴胆碱和LPS对COX2水平的影响。当这些药物在5μM或50μM测试时,可以看出镇痛剂对LPS诱导的反应的抑制效果。

[0358] 表6.在体外用炎症性和非炎症性刺激物刺激和用镇痛剂处理后正常的人膀胱平滑肌细胞的COX2表达

[0359]

刺激物	镇痛剂	总 COX2 水平[#]（标准化的 RFUs）对象 1	总 COX2 水平（标准化的 RFUs）对象 2
无	无	230	199
卡巴胆碱 10^{-3}M	无	437	462
卡巴胆碱 10^{-3}M	对乙酰氨基酚（50μM）	298	310
卡巴胆碱 10^{-3}M	阿司匹林（50μM）	312	297
卡巴胆碱 10^{-3}M	布洛芬（50μM）	309	330
卡巴胆碱 10^{-3}M	萘普生（50μM）	296	354
LPS（10μg/ml）	无	672	633
LPS（10μg/ml）	对乙酰氨基酚（5μM）	428	457
LPS（10μg/ml）	阿司匹林（5μM）	472	491
LPS（10μg/ml）	布洛芬（5μM）	417	456
LPS（10μg/ml）	萘普生（5μM）	458	501
LPS（10μg/ml）	对乙酰氨基酚（50μM）	399	509
LPS（10μg/ml）	阿司匹林（50μM）	413	484
LPS（10μg/ml）	布洛芬（50μM）	427	466
LPS（10μg/ml）	萘普生（50μM）	409	458

[0360] [#] 数据以重复两次的平均值表达

[0361] 镇痛剂抑制正常的人膀胱平滑肌细胞对炎症性和非炎症性刺激物的 PGE2 反应－与上述的对 COX2 反应的诱导相一致，卡巴胆碱和 LPS 均诱导正常的人膀胱平滑肌细胞的 PGE2 的产生。还发现对乙酰氨基酚、阿司匹林、布洛芬和萘普生也在 5μM 或 50μM 下抑制 LPS 诱导的 PGE2 反应（表 7）。

[0362] 表 7. 在体外用炎症性和非炎症性刺激物刺激和用镇痛剂处理后的正常的人膀胱平滑肌细胞的 PGE2 分泌

[0363]

刺激物	镇痛剂	PGE2 水平[#]（pg/ml）对象 1	PGE2 水平（pg/ml）对象 2
无	无	＜20.5	＜20.5
卡巴胆碱 10^{-3}M	无	129	104
卡巴胆碱 10^{-3}M	对乙酰氨基酚（50μM）	76	62
卡巴胆碱 10^{-3}M	阿司匹林（50μM）	89	59
卡巴胆碱 10^{-3}M	布洛芬（50μM）	84	73
卡巴胆碱 10^{-3}M	萘普生（50μM）	77	66
LPS（10μg/ml）	无	1125	998
LPS（10μg/ml）	对乙酰氨基酚（5μM）	817	542
LPS（10μg/ml）	阿司匹林（5μM）	838	598
LPS（10μg/ml）	布洛芬（5μM）	824	527
LPS（10μg/ml）	萘普生（5μM）	859	506
LPS（10μg/ml）	对乙酰氨基酚（50μM）	803	540
LPS（10μg/ml）	阿司匹林（50μM）	812	534
LPS（10μg/ml）	布洛芬（50μM）	821	501
LPS（10μg/ml）	萘普生（50μM）	819	523

[0364] [#] 数据以重复两次的平均值表达

[0365] 镇痛剂抑制正常的人膀胱细胞对炎症性刺激物的细胞因子反应－在培养 24 小时以后的细胞和培养上清液的分析表明，无单独测试的镇痛剂诱导正常的人膀胱平滑肌细胞中的 IL-6 或 TNFα 的分泌。如表 8 和 9 中所示，测试的卡巴胆碱的剂量对正常的人膀胱平滑肌细胞中诱导低但显著的 TNFα 和 IL-6 反应。另一方面，LPS 处理导致这些促炎症反应细胞因子的大量诱导。对乙酰氨基酚、阿司匹林、布洛芬和萘普生均能抑制卡巴胆碱和 LPS 对 TNFα 和 IL-6 反应的影响。当这些药物在 5μM 或 50μM 测试时，可以看出镇痛剂对 LPS 诱导的反应的抑制效果。

[0366] 表 8. 在体外用炎症性和非炎症性刺激物刺激和用镇痛剂处理后正常的人膀胱平滑肌细胞的 TNFα 分泌

[0367]

刺激物	镇痛剂	TNFα（pg/ml）# 对象 1	TNFα（pg/ml）对象 2
无	无	＜5	＜5
卡巴胆碱 10^{-3}M	无	350	286
卡巴胆碱 10^{-3}M	对乙酰氨基酚（50μM）	138	164
卡巴胆碱 10^{-3}M	阿司匹林（50μM）	110	142
卡巴胆碱 10^{-3}M	布洛芬（50μM）	146	121
卡巴胆碱 10^{-3}M	萘普生（50μM）	129	137
LPS（10μg/ml）	无	5725	4107
LPS（10μg/ml）	对乙酰氨基酚（5μM）	2338	2267
LPS（10μg/ml）	阿司匹林（5μM）	2479	2187
LPS（10μg/ml）	布洛芬（5μM）	2733	2288
LPS（10μg/ml）	萘普生（5μM）	2591	2215
LPS（10μg/ml）	对乙酰氨基酚（50μM）	2184	2056
LPS（10μg/ml）	阿司匹林（50μM）	2266	2089
LPS（10μg/ml）	布洛芬（50μM）	2603	1997
LPS（10μg/ml）	萘普生（50μM）	2427	2192

[0368] # 数据以重复两次的平均值表达

[0369] 表 9. 在体外用炎症性和非炎症性刺激物刺激和用镇痛剂处理后正常的人膀胱平滑肌细胞的 IL-6 分泌

[0370]

刺激物	镇痛剂	IL-6（pg/ml）#	IL-6（pg/ml）

[0371]

		对象 1	对象 2
无	无	＜5	＜5
卡巴胆碱 10^{-3}M	无	232	278
卡巴胆碱 10^{-3}M	对乙酰氨基酚（50μM）	119	135
卡巴胆碱 10^{-3}M	阿司匹林（50μM）	95	146
卡巴胆碱 10^{-3}M	布洛芬（50μM）	107	118
卡巴胆碱 10^{-3}M	萘普生（50μM）	114	127
LPS（10μg/ml）	无	4838	4383
LPS（10μg/ml）	对乙酰氨基酚（5μM）	2012	2308
LPS（10μg/ml）	阿司匹林（5μM）	2199	2089
LPS（10μg/ml）	布洛芬（5μM）	2063	2173
LPS（10μg/ml）	萘普生（5μM）	2077	2229
LPS（10μg/ml）	对乙酰氨基酚（50μM）	2018	1983
LPS（10μg/ml）	阿司匹林（50μM）	1987	2010
LPS（10μg/ml）	布洛芬（50μM）	2021	1991
LPS（10μg/ml）	萘普生（50μM）	2102	2028

[0372] # 数据以重复两次的平均值表达

[0373] 将原代的正常的人膀胱平滑肌细胞分离、培养并评价其在非炎症性（卡巴胆碱）和炎症性（LPS）刺激物的存在下对镇痛剂的反应。此研究的目的是确定正常的人膀胱平滑肌细胞是否能重现前述的由鼠科膀胱细胞得到的现象。

[0374] 以延迟释放或延长释放制剂或者延迟和延长释放制剂的镇痛剂和／或抗毒蕈碱剂重复上述实验。

[0375] 上述说明书是用于教导本领域的普通技术人员如何实践本发明目的，其并不意欲详细描述对于本领域的普通技术人员来说阅读了说明书以后能显而易见的那些明显的修改和变化。但是，意欲将所有的明显的修改和变化包括在本发明的范围内，这将通过以下权利要求定义。除非文中有明确的相反指示，权利要求意图覆盖以任何顺序的能够有效实现其所需目的的所要求的组分和步骤。

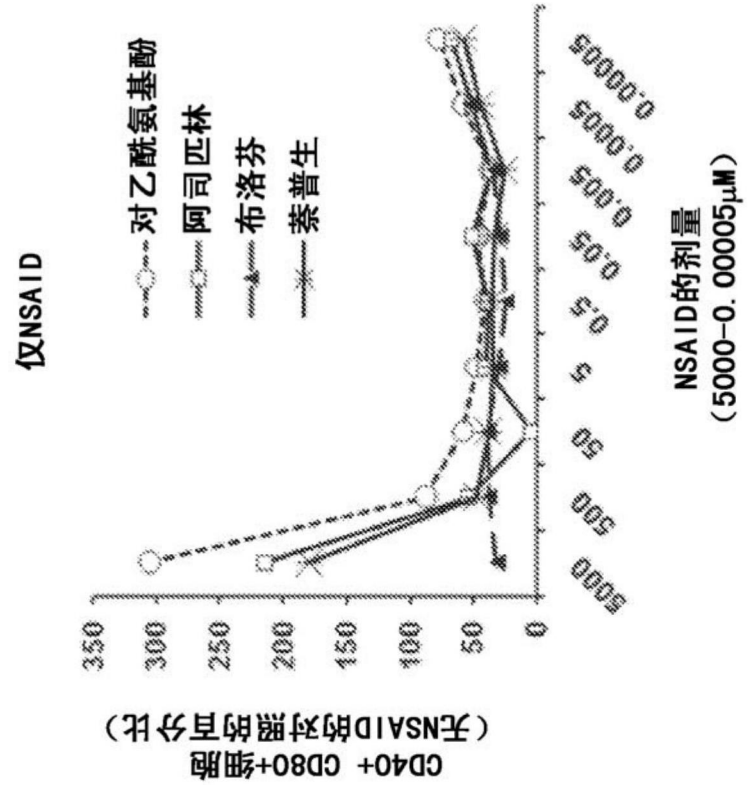

仅NSAID
对乙酰氨基酚
阿司匹林
布洛芬
萘普生
CD40+ CD80+细胞
（无NSAID的对照的百分比）
350
300
250
200
150
100
50
0
5000
500
50
5
0.5
0.05
0.005
0.0005
0.00005
NSAID的剂量
（5000-0.00005μM）

图 1A

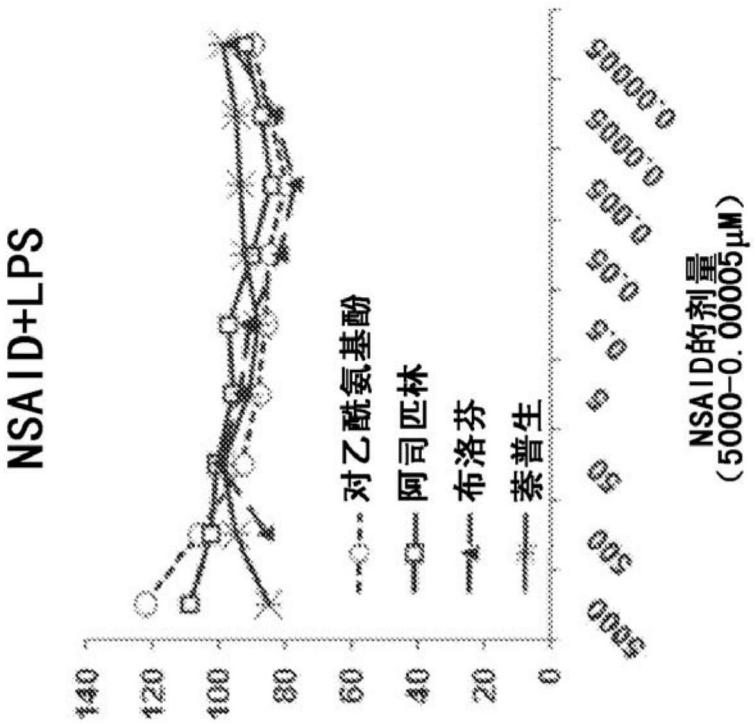

NSAID+LPS
对乙酰氨基酚
阿司匹林
布洛芬
萘普生
140
120
100
80
60
40
20
0
5000
500
50
5
0.5
0.05
0.005
0.0005
0.00005
NSAID的剂量
（5000-0.00005μM）

图 1B

Abstract

A method for reducing the frequency of urination is disclosed. The method comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising one or more analgesic agents and one or more α-blockers. In one embodiment, the one or more analgesic agents are formulated for extended-release.